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(54) Title: METHOD OF TREATING OR PREVENTING SEPTIC SHOCK BY ADMINISTERING A MEK INHIBITOR

(57) Abstract

The present invention provides a method of treating or preventing septic shock. Specifically, the present invention provides a method of treating or preventing septic shock by administering to a patient a MEK inhibitor.

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METHOD OF TREATING OR PREVENTING SEPTIC SHOCK BY ADMINISTERING A MEK INHIBITOR

FIELD OF THE INVENTION

The present invention relates to a method of treating or preventing septic shock in a patient by administering to the patient a compound that is a MEK inhibitor.

BACKGROUND OF THE INVENTION

Septic shock is a serious medical condition that is caused by invasion of the circulatory system by bacteria. Septic shock is characterized by acute circulatory failure, usually with hypotension, followed by multiple organ failure and acute renal failure. The mortality rate of patients having septic shock is in the range of 25% to 90%. It is estimated that up to 500,000 people a year in both the United States and Europe develop septic shock.

The human immune system has many dedicated receptor systems that detect common pathogens, especially bacteria, and these receptor systems are distinct from the specific antibody and T-cell receptor systems, because they are permanently present, and are not tailored to meet a particular threat. Many of the dedicated receptor systems recognize the structural components of bacteria, such as lipopolysaccharide (LPS) lipoteichoic acid and peptidoglycan, and lead to activation of the immune system when these receptors bind structural components of bacteria.

LPS, a major component of the outer cell membrane of gram-negative bacteria, appears to be a major factor in the progression of a bacterial infection to septic shock. The principal mechanism for recognition by the human immune system of LPS is by binding of the CD14 receptor on macrophages to LPS. This binding requires LPS Binding Protein (LBP), an inducible protein made in the liver. Once macrophages have bound and recognized LPS, the macrophages produce massive amounts of inflammatory cytokines, especially tumor necrosis

factor-α (TNF α), Interleukin 1 β (IL-1β), and Interleukin 6 (IL-6).

Three of the transcription factors important in inducing LBP production in the liver are AP-1, C/EBP and STAT-3. All of these can be stimulated through the IL-6 signaling pathway, which is produced locally in the liver by Kuppfer cells. IL-6 stimulates the MAP kinases (also called ERK1 and ERK2) through MEK, and these MAP kinases can activate the three transcription factors mentioned above by phosphorylation. Thus, an inhibitor of MEK can decrease the stimulation of LBP gene transcription, and attenuate the strength of the macrophage response to LPS.

In macrophages, LPS signaling appears to activate all three of the known MAP kinase pathways, including the MEK/ERK cascade, and LPS stimulation of macrophages leads to rapid and major activation of ERKs. ERK is believed to be one of the kinases that phosphorylates IκB, a prerequisite for the liberation of the transcription factor NF κB. NF κB, once liberated, enters the nucleus, and is probably the single most important transcriptional activator for production of TNF α. Thus, an inhibitor of MEK or ERK activity could also decrease the stimulation of TNF-α gene transcription, leading to a greatly decreased physiological response to LPS.

In cells that contain the TNF receptor, activation of that receptor leads to turning on of many pathways that lead to toxicity in the target cell, and which culminate in apoptosis (regulated self-destruction of the cell). Multiple organ failure is more likely caused by TNF-α induced toxicity than by any other single cause. Neutral sphingomyelinase has been shown to be activated by the TNF receptor, and this, in turn, activates ceramide-activated protein kinase, which then activates the MEK/MAP kinase pathway in the target cells, probably adding to the overall toxic effects of TNF.

Thus, the MEK/MAP kinase pathway is important in septic shock, and is involved at several vital points in the progression of septic shock.

SUMMARY OF THE INVENTION

The present invention provides a method of treating or preventing septic shock, the method comprising administering to a patient having septic shock or at risk of having septic shock a therapeutically acceptable amount of a compound that is a MEK inhibitor.

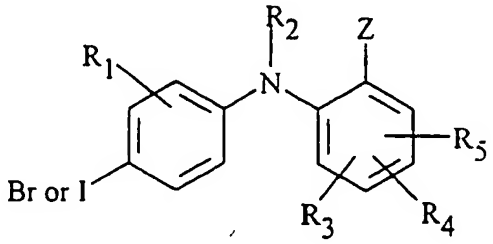
In a preferred embodiment of the invention the MEK inhibitor is 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran.

In another preferred embodiment of the invention, the patient has septic shock.

In another preferred embodiment of the invention, the patient is at risk of having septic shock.

In a more preferred embodiment the invention provides a method of treating or preventing septic shock, the method comprising administering to a patient having septic shock or at risk of having septic shock a therapeutically acceptable amount of 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran.

In a preferred embodiment of the invention, the MEK inhibitor is a compound of Formula I



I

wherein:

R_1 is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN;

R_2 is hydrogen;

R_3, R_4, and R_5 independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, or

-(O or NH)$_m$-(CH$_2$)$_n$-R$_9$, where R$_9$ is hydrogen, hydroxy, COOH, or NR$_{10}$R$_{11}$;

n is 0-4;

m is 0 or 1;

R$_{10}$ and R$_{11}$ independently are hydrogen or C$_1$-C$_8$ alkyl, or taken together with the nitrogen to which they are attached can complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N-C$_1$-C$_8$ alkyl;

Z is COOR$_7$, tetrazolyl, CONR$_6$R$_7$, CONHNR$_{10}$R$_{11}$, or CH$_2$OR$_7$;

R$_6$ and R$_7$ independently are hydrogen, C$_1$-C$_8$ alkyl, C$_2$-C$_8$ alkenyl, C$_2$-C$_8$ alkynyl, C(=O)-C$_1$-C$_8$ alkyl, aryl, heteroaryl, C$_3$-C$_{10}$ cycloalkyl, or C$_3$-C$_{10}$ (cycloalkyl optionally containing one, two, or three heteroatoms selected from O, S, NH, or N alkyl); or R$_6$ and R$_7$ together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl;

and wherein any of the foregoing alkyl, alkenyl, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy, and the pharmaceutically acceptable salts, esters, amides, or prodrugs thereof.

In a more preferred embodiment, the MEK inhibitor is

[4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine;

(4-iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine;

[4-nitro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine;

4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid;

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid;

4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-benzoic acid;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid;

5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid;

2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid;

2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid;

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide;

N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide;

5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

(3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl];

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl- phenylamino)- benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl- phenylamino)- benzamide;

N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

5-Bromo-2-(4-iodo-2-ethyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro- benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide;

N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide;

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-;

5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-;

N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-ethyl-phenylamino)-5-nitro-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol;

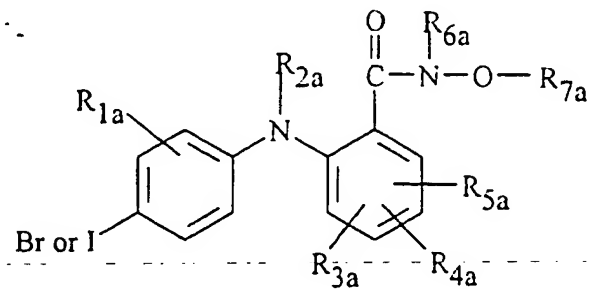
[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol;

[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol;

[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol; or

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide.

In another preferred embodiment, the MEK inhibitor is a compound of Formula II



II

wherein:

R_{1a} is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN;

R_{2a} is hydrogen;

R_{3a}, R_{4a}, and R_{5a} independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, or $(O \text{ or } NH)_m$-$(CH_2)_n$-R_{9a}, where R_{9a} is hydrogen, hydroxy, CO_2H or $NR_{10a}R_{11a}$.

n is 0-4;

m is 0 or 1;

R_{10a} and R_{11a} independently are hydrogen or C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3- to 10-member cyclic ring optionally containing one, two, or three additional heteroatoms selected from O, S, NH, or N-C_1-C_8 alkyl;

R_{6a} is hydrogen, C_1-C_8 alkyl, C-C_1-C_8 alkyl, aryl, aralkyl, or C_3-C_{10} cycloalkyl;

R_{7a} is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{10} (cycloalkyl or cycloalkyl optionally containing a heteroatom selected from O, S, or NR_{9a});

and wherein any of the foregoing alkyl, alkenyl, and alkynyl groups can be unsubstituted or substituted by cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy; or R_{6a} and R_{7a} taken together with the N to which they are attached can complete a 5- to 10-membered cyclic ring, optionally containing one, two, or three additional heteroatoms selected from O, S, or $NR_{10a}R_{11a}$, and the pharmaceutically acceptable salts, esters, amides or prodrugs thereof.

In a more preferred embodiment the MEK inhibitor is

4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(methoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-enyloxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-ethoxy-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1-methylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(propoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclobutyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide;

5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-butoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-but-2-enyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-pent-2-en-4-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-benzyl)-N-[5-(3-methoxy-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[3-(3-methoxy-phenyl)-prop-2-ynyloxy]-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(pyridin-3-ylmethoxy)-benzamide;

5-Bromo-3-4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-but-3-ynyloxy)-benzamide;

5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydro-pyran-2-yloxy)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide;

4-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

5-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydropyran-2-yloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(methoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclobutoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(1-methyl-prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-(3-fluorophenyl)-prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(4,4-dimethylpent-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide;

3,4,5-Trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

N-Hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide;

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Fluoro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-hydroxy-4-methyl-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-Cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide;

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

N-Cyclopropylmethoxy-2-(2-fluoro-4-iodo-phenylamino)-4-nitro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-N-ethoxy-3,4-difluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-ethoxy-4-nitro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-N-cyclopropylmethoxy-3,4-difluoro-benzamide

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzamide;

N-Cyclopropylmethoxy-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-Cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide; or

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method of treating or preventing septic shock, the method comprising administering to a patient having septic shock or at risk of having septic shock a therapeutically acceptable amount of a compound that is a MEK inhibitor.

The patients of the present invention have septic shock or are at risk of having septic shock. Those skilled in the art are readily able to identify patients having septic shock. Moreover, patients who are at risk of having septic shock are also easily identifiable by those skilled in the art. For example, patients who are at risk of having septic shock generally comprise patients who have a bacterial infection. Moreover, the bacterial infection is typically a gram-negative bacterial infection.

The term "patient" means all animals including humans. Examples of patients include humans, cows, dogs, cats, goats, sheep, and pigs.

The compounds of the present invention, which can be used to treat septic shock, are MEK inhibitors. A MEK inhibitor is a compound that shows MEK inhibition when tested in the assays titled "Enzyme Assays" in United States Patent Number 5,525,625, column 6, beginning at line 35. The complete disclosure of United States Patent Number 5,525,625 is hereby incorporated by reference. An example of a MEK inhibitor is 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran. Specifically, a compound is a MEK inhibitor if a compound shows activity in the assay titled "Cascade Assay for Inhibitors of the MAP Kinase Pathway," column 6, line 36 to column 7, line 4 of the United States Patent Number 5,525,625 and/or shows activity in the assay titled "In Vitro MEK Assay" at column 7, lines 4 to 27 of the above-referenced patent.

The MEK inhibitors of the present method can be administered to a patient as part of a pharmaceutically acceptable composition. The compositions can be administered to humans and animals either orally, rectally, parenterally (intravenously, intramuscularly,or subcutaneously), intracisternally, intravaginally, intraperitoneally, intravesically, locally (powders, ointments, or drops), or as a buccal or nasal spray.

Compositions suitable for parenteral injection may comprise physiologically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, and sterile powders for reconstitution into sterile injectable solutions or dispersions. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents, or vehicles include water, ethanol, polyols (propyleneglycol, polyethyleneglycol, glycerol, and the like), suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersions and by the use of surfactants.

These compositions may also contain adjuvants such as preserving, wetting, emulsifying, and dispensing agents. Prevention of the action of microorganisms can be ensured by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, and the like. It may also be desirable to include isotonic agents, for example sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form can be brought about by the use of agents delaying absorption, for example, aluminum monostearate and gelatin.

Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is admixed with at least one inert customary excipient (or carrier) such as sodium citrate or dicalcium phosphate or (a) fillers or extenders, as for example, starches, lactose, sucrose, glucose, mannitol, and silicic acid, (b) binders, as for example, carboxymethylcellulose, alignates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, (c) humectants, as for example, glycerol, (d) disintegrating agents, as for example, agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain complex silicates, and sodium carbonate, (e) solution retarders, as for example paraffin, (f) absorption accelerators, as for example, quaternary ammonium compounds, (g) wetting agents, as for example, cetyl alcohol and glycerol monostearate, (h) adsorbents, as for example, kaolin and bentonite, and (i) lubricants, as for example, talc, calcium stearate, magnesium stearate, solid

polyethylene glycols, sodium lauryl sulfate, or mixtures thereof. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethyleneglycols, and the like.

Solid dosage forms such as tablets, dragees, capsules, pills, and granules can be prepared with coatings and shells, such as enteric coatings and others well-known in the art. They may contain opacifying agents, and can also be of such composition that they release the active compound or compounds in a certain part of the intestinal tract in a delayed manner. Examples of embedding compositions which can be used are polymeric substances and waxes. The active compounds can also be in micro-encapsulated form, if appropriate, with one or more of the above-mentioned excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art, such as water or other solvents, solubilizing agents and emulsifiers, as for example, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propyleneglycol, 1,3-butyleneglycol, dimethylformamide, oils, in particular, cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, tetrahydrofurfuryl alcohol, polyethyleneglycols, and fatty acid esters of sorbitan or mixtures of these substances, and the like.

Besides such inert diluents, the composition can also include adjuvants, such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

Suspensions, in addition to the active compounds, may contain suspending agents, as for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, or mixtures of these substances, and the like.

Compositions for rectal administrations are preferably suppositories which can be prepared by mixing the compounds of the present invention with suitable

non-irritating excipients or carriers such as cocoa butter, polyethyleneglycol, or a suppository wax, which are solid at ordinary temperatures but liquid at body temperature and therefore, melt in the rectum or vaginal cavity and release the active component.

Dosage forms for topical administration of a compound of this invention include ointments, powders, sprays, and inhalants. The active component is admixed under sterile conditions with a physiologically acceptable carrier and any preservatives, buffers, or propellants as may be required. Ophthalamic formulations, eye ointments, powders, and solutions are also contemplated as being within the scope of this invention.

The compounds of the present method can be administered to a patient at dosage levels in the range of about 0.1 to about 1000 mg per day. For a normal human adult having a body weight of about 70 kg, a dosage in the range of about 0.01 to about 100 mg per kg of body weight per day is preferable. The specific dosage used, however, can vary. For example, the dosage can depend on a numbers of factors including the requirements of the patient, the severity of the condition being treated, and the pharmacological activity of the compound being used. The determination of optimum dosages for a particular patient is well-known to those skilled in the art.

The compounds of the present method can be administered as pharmaceutically acceptable salts, esters, amides, or prodrugs. The term "pharmaceutically acceptable salts, esters, amides, and prodrugs" as used herein refers to those carboxylate salts, amino acid addition salts, esters, amides, and prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of patients without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "salts" refers to the relatively non-toxic, inorganic and organic acid addition salts of compounds of the present invention. These salts can be prepared *in situ* during the final isolation and purification of the compounds or by separately reacting the purified compound in its free base form with a suitable organic or

inorganic acid and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, nitrate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate mesylate, glucoheptonate, lactiobionate and laurylsulphonate salts, and the like. These may include cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium and the like, as well as nontoxic ammonium, quaternary ammonium, and amine cations including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. (See, for example, S.M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1977;66:1-19 which is incorporated herein by reference.)

Examples of pharmaceutically acceptable, non-toxic esters of the compounds of this invention include C_1-C_6 alkyl esters wherein the alkyl group is a straight or branched chain. Acceptable esters also include C_5-C_7 cycloalkyl esters as well as arylalkyl esters such as, but not limited to benzyl. C_1-C_4 alkyl esters are preferred. Esters of the compounds of the present invention may be prepared according to conventional methods.

Examples of pharmaceutically acceptable, non-toxic amides of the compounds of this invention include amides derived from ammonia, primary C_1-C_6 alkyl amines and secondary C_1-C_6 dialkyl amines wherein the alkyl groups are straight or branched chain. In the case of secondary amines the amine may also be in the form of a 5 or 6 membered heterocycle containing one nitrogen atom. Amides derived from ammonia, C_1-C_3 alkyl primary amines and C_1-C_2 dialkyl secondary amines are preferred. Amides of the compounds of the invention may be prepared according to conventional methods.

The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example, by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, ed. Edward B.

Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

In addition, the compounds of the present method can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of the present invention.

The compounds of the present method can exist in different stereoisometric forms by virtue of the presence of asymmetric centers in the compounds. It is contemplated that all stereoisometric forms of the compounds as well as mixtures thereof, including racemic mixtures, form part of this invention.

As used herein, the term "aryl" means a cyclic, bicyclic, or tricyclic aromatic ring moiety having from five to twelve carbon atoms. Examples of typical aryl groups include phenyl, naphthyl, and fluorenyl. The aryl may be substituted by one, two, or three groups selected from fluoro, chloro, bromo, iodo, alkyl, hydroxy, alkoxy, nitro, amino, alkylamino, or dialkylamino. Typical substituted aryl groups include 3-fluorophenyl, 3,5-dimethoxyphenyl, 4-nitronaphthyl, 2-methyl-4-chloro-7-aminofluorenyl, and the like.

The term "aryloxy" means an aryl group bonded through an oxygen atom, for example phenoxy, 3-bromophenoxy, naphthyloxy, and 4-methyl-1-fluorenyloxy.

"Heteroaryl" means a cyclic, bicyclic, or tricyclic aromatic ring moiety having from four to eleven carbon atoms and one, two, or three heteroatoms selected from O, S, or N. Examples include furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, xanthenyl, pyronyl, indolyl, pyrimidyl, naphthyridyl, pyridyl, benzinnidazolyl, and triazinyl. The heteroaryl groups can be unsubstituted or substituted by one, two, or three groups selected from fluoro, chloro, bromo, iodo, alkyl, hydroxy, alkoxy, nitro, amino, alkylamino, or dialkylamino. Examples of substituted heteroaryl groups include chloropyranyl, methylthienyl, fluoropyridyl, amino-1,4-benzisoxazinyl, nitroisoquinolinyl, and hydroxyindolyl.

The heteroaryl groups can be bonded through oxygen to make heteroaryloxy groups, for example thienyloxy, isothiazolyloxy, benzofuranyloxy, pyridyloxy, and 4-methylisoquinolinyloxy.

The term "alkyl" means straight and branched chain aliphatic groups. Typical alkyl groups include methyl, ethyl, isopropyl, tert.-butyl, 2,3-dimethylhexyl, and 1,1-dimethylpentyl. The alkyl groups can be unsubstituted or substituted by halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy, as those terms are defined herein. Typical substituted alkyl groups include chloromethyl, 3-hydroxypropyl, 2-dimethylaminobutyl, and 2-(hydroxymethylamino)ethyl. Examples of aryl and aryloxy substituted alkyl groups include phenylmethyl, 2-phenylethyl, 3-chlorophenylmethyl, 1,1-dimethyl-3-(2-nitrophenoxy)butyl, and 3,4,5-trifluoronaphthylmethyl. Examples of alkyl groups substituted by a heteroaryl or heteroaryloxy group include thienylmethyl, 2-furylethyl, 6-furyloxyoctyl, 4-methylquinolyloxymethyl, and 6-isothiazolylhexyl. Cycloalkyl substituted alkyl groups include cyclopropylmethyl, 2-cyclohexyethyl, piperidyl-2-methyl, 2-(piperidin-1-yl)-ethyl, 3-(morpholin-4-yl)propyl.

"Alkenyl" means a straight or branched carbon chain having one or more double bonds. Examples include but-2-enyl, 2-methyl-prop-2-enyl, 1,1-dimethyl-hex-4-enyl, 3-ethyl-4-methyl-pent-2-enyl, and 3-isopropyl-pent-4-enyl. The alkenyl groups can be substituted with halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, aryl, aryloxy, heteroaryl, or heteroyloxy, for example 2-bromoethenyl, 3-hydroxy-2-butenyl, 1-aminoethenyl, 3-phenylprop-2-enyl, 6-thienyl-hex-2-enyl, 2-furyloxy-but-2-enyl, and 4-naphthyloxy-hex-2-enyl.

"Alkynyl" means a straight or branched carbon chain having at least one triple bond. Typical alkynyl groups include prop-2-ynyl, 2-methyl-hex-5-ynyl, 3,4-dimethyl-hex-5-ynyl, and 2-ethyl-but-3-ynyl. The alkynyl groups can be substituted as the alkyl and alkenyl groups, for example, by aryl, aryloxy, heteroaryl, or heteroaryloxy, for example 4-(2-fluorophenyl)-but-3-ynyl, 3-methyl-5-thienylpent-4-ynyl, 3-phenoxy-hex-4-ynyl, and 2-furyloxy-3-methyl-hex-4-ynyl.

The alkenyl and alkynyl groups can have one or more double bonds or triple bonds, respectively, or a combination of double and triple bonds. For

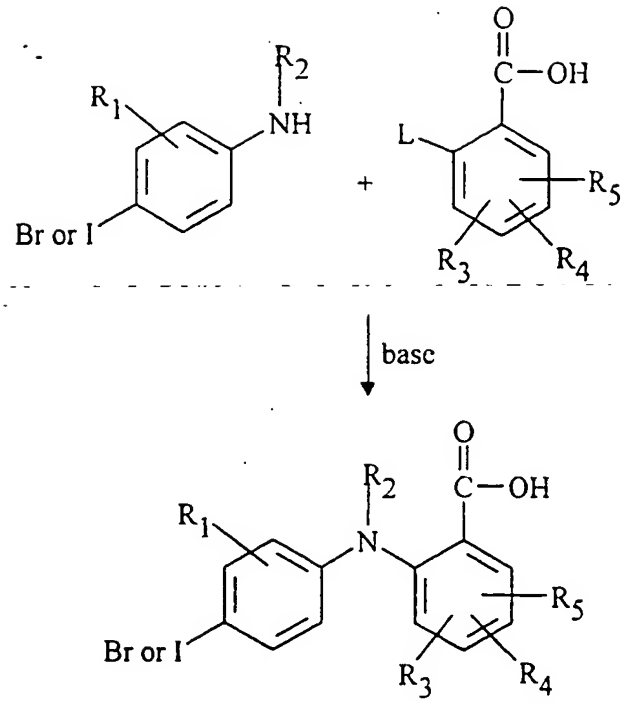
example, typical groups having both double and triple bonds include hex-2-en-4-ynyl, 3-methyl-5-phenylpent-2-en-4-ynyl, and 3-thienyloxy-hex-3-en-5-ynyl.

The term "cycloalkyl" means a nonaromatic ring or fused rings. Examples include cyclopropyl, cyclobutyl, cyclopenyl, cyclooctyl, bicycloheptyl, adamantyl, and cyclohexyl. The ring can optionally contain one, two, or three heteroatoms selected from O, S, or N. Such groups include tetrahydrofuryl, tetrahydropyrrolyl, octahydrobenzofuranyl, morpholinyl, piperazinyl, pyrrolidinyl, piperidinyl, octahydroindolyl, and octahydrobenzothiofuranyl. The cycloalkyl groups can be substituted with the same substituents as an alkyl and alkenyl groups, for example, halo, hydroxy, aryl, and heteroaryloxy. Examples include 3-hydroxycyclohexyl, 2-aminocyclopropyl, 2-phenylpyrrolidinyl, and 3-thienylmorpholine-1-yl.

The examples presented below are intended to illustrate particular embodiments of the invention and are not intended to limit the scope of the specification, including the claims, in any way.

The 2-(4-bromo and 4-iodo phenylamino)-benzoic acid derivatives of Formula I can be prepared from commercially available starting materials utilizing synthetic methodologies well-known to those skilled in organic chemistry. A typical synthesis is carried out by reacting a 4-bromo or 4-iodo aniline with a benzoic acid having a leaving group at the 2-position to give a 2-(phenylamino)-benzoic acid. This process is depicted in Scheme 1.

Scheme 1



where L is a leaving group, for example halo such as fluoro.

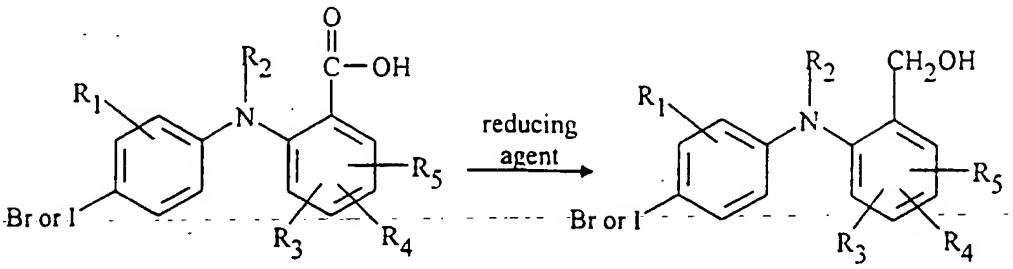
The reaction of aniline and the benzoic acid derivative generally is accomplished by mixing the benzoic acid with an equimolar quantity or excess of the aniline in an unreactive organic solvent such as tetrahydrofuran or toluene, in the presence of a base such as lithium diisopropylamide, n-butyl lithium, sodium hydride, triethylamine, and Hunig's base. The reaction generally is carried out at a temperature of about -78°C to about 100°C, and normally is complete within about 2 hours to about 4 days. The product can be isolated by removing the solvent, for example by evaporation under reduced pressure, and further purified, if desired, by standard methods such as chromatography, crystallization, or distillation.

The 2-(phenylamino)-benzoic acid (e.g., Formula I, where R_7 is hydrogen) can be reacted with an organic or inorganic base such as pyridine, triethylamine, calcium carbonate, or sodium hydroxide to produce a pharmaceutically acceptable

salt. The free acids can also be reacted with an alcohol of the formula HOR_7 (where R_7 is other than hydrogen, for example methyl) to produce the corresponding ester. Reaction of the benzoic acid with an alcohol can be carried out in the presence of a coupling agent. Typical coupling reagents include 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 1,3-dicyclohexylcarbodiimide (DCC), bromo-tris(pyrrolidino)- phosphonium hexafluorophosphate (PyBrOP), and (benzotriazolyloxy) tripyrrolidino phosphonium hexafluorophosphate (PyBOP). The phenylamino benzoic acid and alcohol derivative normally are mixed in approximately equimolar quantities in an unreactive organic solvent such as dichloromethane, tetrahydrofuran, chloroform, or xylene, and an equimolar quantity of the coupling reagent is added. A base such as triethylamine or diisopropylethylamine can be added to act as an acid scavenger if desired. The coupling reaction generally is complete after about 10 minutes to 2 hours, and the product is readily isolated by removing the reaction solvent, for instance by evaporation under reduced pressure, and purifying the product by standard methods such as chromatography or crystallizations from solvents such as acetone, diethyl ether, or ethanol.

The benzamides of the invention, Formula I where Z is $CONR_6R_7$, are readily prepared by reacting the foregoing benzoic acids with an amine of the formula HNR_6R_7. The reaction is carried out by reacting approximately equimolar quantities of the benzoic acid and amine in an unreactive organic solvent in the presence of a coupling reagent. Typical solvents are chloroform, dichloromethane, tetrahydrofuran, benzene, toluene, and xylene. Typical coupling reagents include DCC, EEDQ, PyBrOP, and PyBOP. The reaction is generally complete after about 10 minutes to about 2 hours when carried out at a temperature of about 0°C to about 60°C. The product amide is readily isolated by removing the reaction solvent, for instance by evaporation, and further purification can be accomplished by normal methods such as chromatography, crystallization, or distillation. The hydrazides (z = $CONHNR_{10}R_{11}$) are similarly prepared by coupling a benzoic acid with a hydrazine of the formula $H_2HNR_{10}R_{11}$.

The benzyl alcohols of the invention, compounds of Formula I where Z is CH_2OR_6 and R_6 is hydrogen, are readily prepared by reduction of the corresponding benzoic acid according to the following scheme



Typical reducing agents commonly employed include borane in tetrahydrofuran. The reduction normally is carried out in an unreactive organic solvent such as tetrahydrofuran, and generally is complete within about 2 hours to about 24 hours when conducted at a temperature of about 0°C to about 40°C.

The following detailed examples illustrate specific compounds provided by this invention.

EXAMPLE 1

4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid

To a stirring solution comprised of 3.16 g (0.0133 mol) of 2-amino-5-iodotoluene in 5 mL of tetrahydrofuran at -78°C was added 10 mL (0.020 mol) of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethenylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for 15 minutes, after which time a solution of 1.00 g (0.00632 mol) of 2,4-difluorobenzoic acid in 10 mL of tetrahydrofuran was added. The reaction temperature was allowed to increase slowly to room temperature, at which temperature it was stirred for 2 days. The reaction mixture was concentrated. Aqueous HCl (10%) was added to the concentrate, and the solution was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and then boiled over a steambath to low volume and cooled to room temperature. The off-white fibers were collected by vacuum filtration, rinsed with hexanes, and vacuum-oven

dried. (76°C; ca. 10 mm of Hg) to afford 1.10 g (47%) of the desired material; mp 224-229.5°C;

^{1}H NMR (400 MHz; DMSO): δ 9.72 (s, 1H), 7.97 (dd, 1H, J = 7.0, 8.7 Hz), 7.70 (d, 1H, J = 1.5 Hz), 7.57 (dd, 1H, J = 8.4, 1.9 Hz), 7.17 (d, 1H, J = 8.2 Hz), 6.61-6.53 (m, 2H), 2.18 (s, 3H);

^{13}C NMR (100 MHz; DMSO): δ 169.87, 167.60, 165.12, 150.17, 150.05, 139.83, 138.49, 136.07, 135.31, 135.20, 135.07, 125.60, 109.32, 105.09, 104.87, 99.72, 99.46, 89.43, 17.52;

^{19}F NMR (376 MHz; DMSO): δ -104.00 to -104.07 (m);

IR (KBr) 1670 (C = O stretch) cm^{-1};

MS (CI) M+1 = 372.

Analysis calculated for $C_{14}H_{11}FINO_2$:

C, 45.31; H, 2.99; N, 3.77.

Found: C, 45.21; H, 2.77; N, 3.64.

EXAMPLES 2-30

By following the general procedure of Example 1, the following benzoic acids and salts were prepared:

Example No.	Compound	MP °C
2	3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	206-210
3	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	240.5-244.5
4	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	259.5-262

Example No.	Compound	MP °C
5	5-Chloro-2-(2-chloro-4-iodo-phenylamino)-benzoic acid	255-260
6	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	234-238
7	Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate	310-320 DEC
8	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	239.5-240
9	2-(2-Chloro-4-iodo-phenylamino)-5-nitro-benzoic acid	289-293
10	4-Fluoro-2-(3-fluoro-4-iodo-2-methyl-phenylamino)-benzoic acid	233-235
11	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid	264-267
12	2-(2-Fluoro-4-iodo-phenylamino)-5-nitro-benzoic acid	256-258
13	2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid	218.5-220
14	2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid	285-288 DEC
15	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid	230-234
16	3-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	218-221
17	3,4-Difluoro-2-(4-iodo-2-methoxy-phenylamino)-benzoic acid	230-233
18	4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	245-255 DEC

Example No.	Compound	MP °C
19	2-(4-Iodo-2-methyl-phenylamino)-benzoic acid	218-223
20	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	243-46
21	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	241-245
22	2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid	218-222
23	4-Fluoro-2-(3-chloro-4-iodo-2-methyl-phenylamino)-benzoic acid	248-252.5
24	2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid	208-211
25	3-Chloro-2-(2-chloro-4-iodo-phenylamino)-benzoic acid	232-233
26	2-Fluoro-6-(4-iodo-2-methyl-phenylamino)-benzoic acid	179-182
27	4-Fluoro2-(2,3-dimethyl-4-iodo-2-methyl-phenylamino)benzoic acid	258-261
28	5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid	209.5-211
29	2-Chloro-6-(4-iodo-2-methyl-phenylamino)-benzoic acid	171-175
30	2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid	251-263

EXAMPLE 31

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a stirring solution comprised of 0.1020 g (0.2632 mmol) of 5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid, 0.1 mL (1.7 mmol) of ethanolamine, and 0.05 mL (0.29 mmol) of diisopropylethylamine in 5 mL of a 1:1 (v/v) tetrahydrofuran-dichloromethane solution was added 0.15 g (0.29 mmol)

of solid PyBOP powder directly. The reaction mixture was stirred at room temperature overnight. The solvent was removed in vacuo. The crude residue was partitioned between ether (50 mL) and 10% aqueous hydrochloric acid (50 mL). The organic phase was washed with 10% aqueous sodium hydroxide (50 mL), dried ($MgSO_4$) and concentrated in vacuo to afford a yellow-brown oil which was crystallized from hexanes-ether to afford 0.0831 g (73%) of a green-yellow powder; mp 120-121°C;

^1H NMR (400 MHz; $CDCl_3$): δ 9.11 (s, 1H), 7.56 (d, 1H, J = 1.4 Hz), 7.46-7.41 (m, 2H), 7.20 (dd, 1H, J = 8.9, 2.4 Hz), 7.00 (t, 2H, J = 9.6 Hz), 6.55 (broad t, 1H), 3.86 (t, 2H, J = 5.0 Hz), 3.61 (dd, 2H, J = 10.1, 5.5 Hz), 2.23 (s, 3H), 1.56 (broad s, 1H);

IR (KBr) 3297 (O-H stretch), 1627 (C = O stretch) cm^{-1};

MS (CI) M+1 = 431.

Analysis calculated for $C_{16}H_{16}ClIN_2O_2$:

C, 44.62; H, 3.74; N, 6.50.

Found: 44.63; H, 3.67; N, 6.30.

EXAMPLES 32-48

By following the general procedure of Example 31, the following benzamides were prepared by reacting the corresponding benzoic acid with the corresponding amine.

Example No.	Compound	MP °C
32	4-Methoxy-N-(4-methoxy-phenyl)-3-nitro-benzamide	153.5-156
33	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	158
34	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide	102.5-104.5

Example No.	Compound	MP °C
35	N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	90-91
36	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	oil
37	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide	285-288 DEC
38	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	180-182
39	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	137-138
40	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid	170-173
41	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide	69-71
42	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	132-133.4
43	N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	oil
44	4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide	122-124
45	N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	91-93
46	N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	97-99
47	5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	118-120
48	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide	142.5-144

EXAMPLE 49

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (0.50 g, 1.35 mmol) was dissolved in 6 mL (6 mmol) of cold 1.0 M borane-tetrahydrofuran complex in tetrahydrofuran solution. The reaction mixture was stirred under nitrogen atmosphere at room temperature overnight. The reaction was quenched with 80 mL of methanol. Concentration in vacuo produced a clear tan oil which was purified by MPLC. Elution with dichloromethane afforded 0.4285 g (89%) of a white solid; mp 99-100.5°C;

^{1}H NMR (400 MHz; DMSO): δ 7.57 (d, 1H, J=1.7 Hz), 7.45 (dd, 1H, J=8.4, 1.9 Hz), 7.39 (s, 1H), 7.29 (t, 1H, J=7.5 Hz), 6.89 (d, 1H, J=8.4 Hz), 6.67-6.60 (m, 1H), 5.47 (t, 1H, J=5.5 Hz), 4.49 (d, 2H, 5.1 Hz), 2.14 (s, 3H);

IR (KBr) 3372 (O-H stretch) cm^{-1};

MS (CI) M+1 = 358.

Analysis calculated for $C_{14}H_{13}FINO$:

C, 47.08; H, 3.67; N, 3.92.

Found: C, 47.17; H, 3.75; N, 3.72.

EXAMPLE 50-52

The following benzyl alcohols were prepared by the general procedure of Example 49.

Example No.	Compound	MP °C
50	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol	82-85
51	[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol	126.5-128.5
52	[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol	60.5-63.5

Several invention compounds of Formula I were prepared utilizing combinatorial synthetic techniques. The general procedure is as follows:

To a 0.8-mL autosampler vial in a metal block was added 40 µL of a 0.5 M solution of the acid in DMF and 40 µL of the reagent amine (2 M solution in Hunig's base and 1 M in amine in DMF). A 0.5 M solution of PyBrop was freshly prepared and 50 µL were added to the autosampler vial. The reaction was allowed to stand for 24 hours.

The reaction mixture was transferred to a 2-dram vial and diluted with 2 mL of ethyl acetate. The organic layer was washed with 3 mL of distilled water and the water layer washed again with 2 mL of ethyl acetate. The combined organic layers were allowed to evaporate to dryness in an open fume hood.

The residue was taken up in 2 mL of 50% acetonitrile in water and injected on a semi-prep reversed phase column (10 mm × 25 cm, 5 µM spherical silica, pore size 115 A derivatized with C-18, the sample was eluted at 4.7 mL/min with a linear ramp to 100% acetonitrile over 8.5 minutes. Elution with 100% acetonitrile continued for 8 minutes). Fractions were collected by monitoring at 214 nM. The residue was dissolved in chloroform and transferred to a preweighed vial, evaporated, and weighed again to determine the yield.

EXAMPLES 53-206

The following compounds of Formula I were prepared by combinatorial methodology:

Example No.	Compound	MS M-H
53	5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	510
54	N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	462

Example No.	Compound	MS M-H
55	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	577
56	3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	432
57	N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	444
58	3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	446
59	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	564
60	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	571
61	4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	414
62	5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	551
63	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	580
64	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	501
65	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	485
66	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	493
67	N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	473
68	N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	460
69	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide	384
70	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	483

Example No.	Compound	MS M-H
71	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	495
72	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	513
73	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide	480
74	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	467
75	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide	453
76	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	557
77	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	479
78	2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide	425
79	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	461
80	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide	475
81	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide	445
82	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-benzamide	400
83	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	437
84	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide	474
85	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide	450
86	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide	431

Example No.	Compound	MS M-H
87	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide	.444
88	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide	451
89	5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide	557*
90	5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide	541*
91	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide	487
92	5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide	601*
93	5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide	486*
94	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	497*
95	(3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl]-	466
96	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	484*
97	5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide	530*
98	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl- phenylamino)- benzamide	518*
99	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl- phenylamino)- benzamide	562*
100	[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-	499
101	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid phenethyl ester	501
102	N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide	568*

Example No.	Compound	MS M-H
103	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-	455
104	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide	460
105	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	528*
106	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	542*
107	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	468*
108	5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	472*
109	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl- phenylamino)- benzamide	502*
110	5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	445*
111	5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide	516*
112	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide	482*
113	5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	489*
114	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	556*
115	N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro- benzamide	529*
116	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	500*
117	5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	500*

Example .No.	Compound	MS M-H
118	5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	514*
119	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	512*
120	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide	509*
121	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide	544*
122	N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	470*
123	5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	516*
124	N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	456*
125	5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	429*
126	N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	484*
127	N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	511*
128	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	544*
129	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide	523*
130	[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-	439
131	5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	558*
132	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide	484*
133	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide	496*

Example No.	Compound	MS M-H
134	[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-	482
135	N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide	500*
136	[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid	443
137	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide	495*
138	N-(3-Dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	483*
139	N-(2-Diisopropylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide	498*
140	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-phenethyl ester	490
141	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-phenethyl ester	506
142	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	536
143	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-thiobenzoic acid S-benzyl ester	503
144	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	476
145	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-thiobenzoic acid S-benzyl ester	492
146	N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	409
147	5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	429
148	5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	413
149	N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	475

Example No.	Compound	MS M-H
150	N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	593*
151	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide	567
152	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	473
153	N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	521
154	N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	440
155	2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide	486
156	5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
157	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	459
158	N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	409
159	N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	583
160	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	538
161	N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
162	N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	436
163	5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	469
164	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	475
165	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	646
166	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	598
167	N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	436

Example No.	Compound	MS M-H
168	2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide	565
169	N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	469
170	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	473
171	N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	517
172	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	519
173	N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	502
174	N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	559
175	N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	517
176	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	581
177	2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide	500
178	5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	567
179	N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	451
180	5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	467
181	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	533
182	5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	511
183	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide	489
184	N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	478

Example No.	Compound	MS M-H
185	N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	538
186	N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	477
187	5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	431
188	5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	475
189	2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide	488
190	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	477
191	N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	523
192	5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	425
193	N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide	427
194	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	461
195	N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	442
196	5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide	415
197	5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide	472
198	N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	411
199	5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	540
200	N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	438
201	N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide	411

Example No.	Compound	MS M-H
202	N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide	585
203	N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide	472
204	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide	601
205	5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide	522
206	N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide	438

* M+H

EXAMPLE 207

Preparation of [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine

Step a: Preparation of 5-chloro-2-fluoro-benzaldehyde

To a solution of 1-chloro-4-fluorobenzne (13.06 g, 0.1 mol) in THF (180 mL), at -78°C, LDA (2M solution in THF, 50 mL, 0.1 mol) was added drop wise. After stirring at -78°C for 1.5 hours, DMF (8 mL) was added to the reaction mixture and allowed to warm up to room temperature overnight. The reaction mixture was partitioned between water and Et_2O. The Et_2O layer was dried ($MgSO_4$) and the solvent removed in vacuum to give 14.95 g (94%) yield of crude aldehyde:

^1H NMR ($CDCl_3$): δ, 10.3 (s, -C(=O)H).

Step b: Preparation of 5-chloro-2-fluoro-benzaldehyde oxime

A solution of 5-chloro-2-fluoro-benzaldehyde (10 g, 0.0631 mol), hydroxylamine hydrochloride (6.57 g, 0.0946 mol) and pyridine (8.3 mL, 0.1010 mol) in EtOH (100 mL) was heated at 75°C (oil bath temperature) for 1 hour and the solvent removed under vacuum to give an oil. The oil was partitioned between water and CH_2Cl_2. The CH_2Cl_2 layer was dried ($MgSO_4$) and the solvent removed under vacuum to give crude aldoxime as a solid. The

solid was purified by medium pressure liquid chromatography on silica. Elution with CH_2Cl_2 gave 4:87 g (28%) of the aldoxime as white solid: mp 95-97°C;

Analysis calculated for C_7H_5NOFCl:

C, 48.44; H, 2.90; N, 8.07.

Found: C, 48.55; H, 2.69, N, 7.90.

Step c: Preparation of 5-chloro-2-fluoro-benzonirile

A solution of the 5-chloro-2-fluoro-benzaldehyde oxime (3.15 g, 0.0182 mol) in acetic anhydride (150 mL) was refluxed for 16 hours. The reaction mixture was cooled to room temperature and poured into saturated aqueous $NaHCO_3$ (200 mL) solution. The mixture was extracted with Et_2O. The Et_2O layer was dried (K_2CO_3) and the solvent removed to give the product as an oily solid. The product was used without further purification in the next step.

Step d: Preparation of 5-(5-chloro-2-fluoro-phenyl)-1H-tetrazole

A mixture of 5-chloro-2-fluoro-benzonitrile (2.84 g, 0.01823 mol), butanol (15 mL), sodium azide (1.543 g, 0.0237 mol), acetic acid (1.36 mL, 0.0237 mol) was refluxed for 24 hours. The reaction mixture was cooled to room temperature, additional 1.543 g sodium azide added, and the reaction mixture refluxed for additional 24 hours. After cooling to room temperature, Et_2O (100 mL) and 10% aqueous NaOH (200 mL) were added sequentially. The mixture was vigorously stirred. The aqueous layer was separated, cooled with ice-methanol bath (-15°C) and acidified to pH 1 with conc. HCl. A gray solid precipitated. The solid was dried in vacuum at 50°C to give 1.76 g (49%) of 5-(5-chloro-2-fluoro-phenyl)-1H-tetrazole: mp partial melt at 110°C, complete melting at 124°C);

^1H (400 Mz, $CDCl_3$): δ 8.19-8.08 (m, 1H), 7.77-7.71 (m, 1H), 7.61-7.52 (m, 1H);

^{13}C (100 Mz, $CDCl_3$): δ 159.00, 156.49, 140.88, 133.02, 132.93, 130.73, 129.23, 129.21, 129.08, 126.05, 118.96, 118.73, 114.50;

MS (CI) M+1 = 199 (100), M = 198 (6).

Step e: Preparation of [4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine

To a solution of 2-methyl-4-iodoaniline (3.52 g, 0.0151 mol) in THF (25 mL) at -78°C, LDA (2 molar solution in THF, 11.33 mL, 0.02267 mol) was added dropwise. After stirring for 0.5 hours, a solution of 1-(tetrazol-5-yl)-2-fluoro-5-chlorobenzene (1.5 g, 0.00756 mol) in THF (15 mL) was added dropwise. The reaction was stirred for 16 hours as it warmed up to room temperature. The reaction mixture was quenched with aqueous conc. NH_4Cl solution and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent removed giving a crude product as an oil. The oil with CH_2Cl_2->CH_2Cl_2:MeOH (9.7:0.3) gave 1.5 g (48%) of the desired product:

mp 205-208°C;

^1H (400 Mz, DMSO): δ 9.13 (s, 1H), 8.00-7.99 (s, 1H), 7.69 (s, 1H), 7.55-7.52 (m, 1H), 7.43-7.40 (m, 1H), 7.12-7.05 (m, 1H), 2.24 (s, 3H);

^{13}C (100 Mz, $CDCl_3$): δ 141.87, 139.28, 138.88, 135.47, 133.71, 131.65, 128.15, 123.69, 121.94, 116.68, 87.79, 17.22;

MS (Cl) M+2 = 413 (44), M+1 = 412 (85), M = 411 (100).

Analysis calculated for $C_{14}H_{11}N_5ClI \cdot 0.5H_2O$:

C, 39.97; H, 2.87; N, 16.65.

Found: C, 38.87, H, 2.77; N, 16.47.

The following tetrazole substituted phenylamines were prepared by following the general procedure of Example 207.

EXAMPLE 208

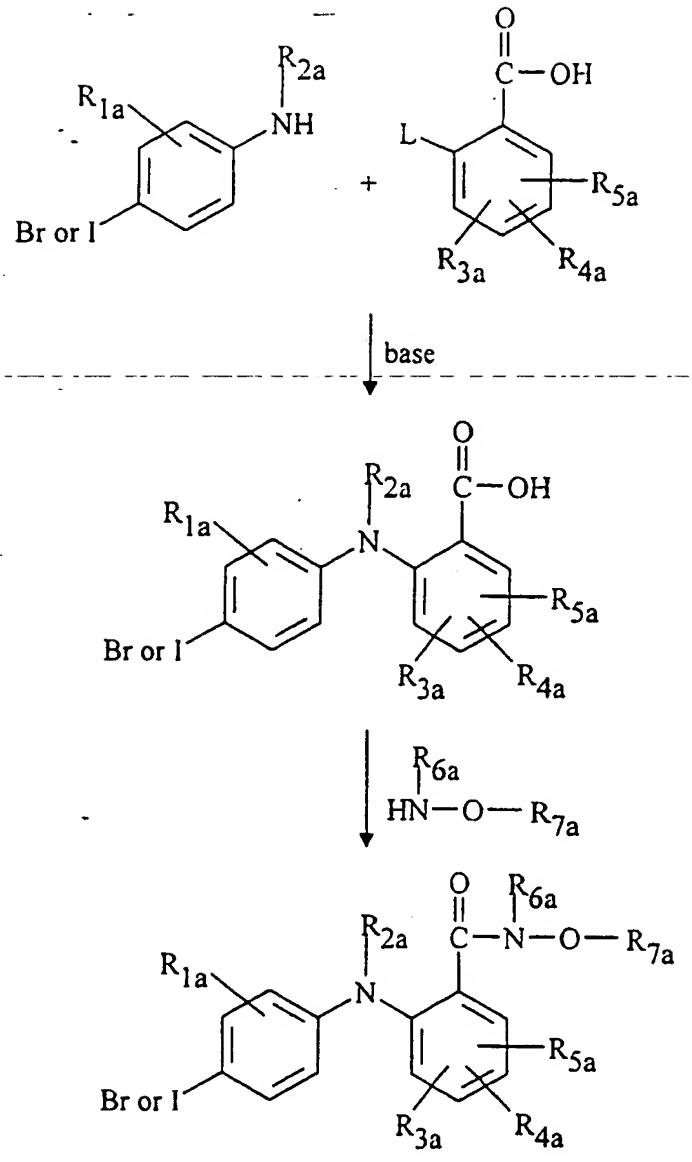
(4-iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine, mp 231°C (dec)

EXAMPLE 209

[4-nitro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine, mp 205-208°C.

The 4-bromo and 4-iodo phenylamino benzhydroxamic acid derivatives of Formula I can be prepared from commercially available starting materials utilizing synthetic methodologies well-known to those skilled in organic chemistry. A typical synthesis is carried out by reacting a 4-bromo or 4-iodo aniline with a benzoic acid having a leaving group at the 2-position to give a phenylamino benzoic acid, and then reacting the benzoic acid phenylamino derivative with a hydroxylamine derivative. This process is depicted in Scheme 1a.

Scheme 1a



where L is a leaving group, for example halo such as fluoro, chloro, bromo or iodo, or an activated hydroxy group such as a diethylphosphate, trimethylsilyloxy, p-nitrophenoxy, or phenylsulfonoxy.

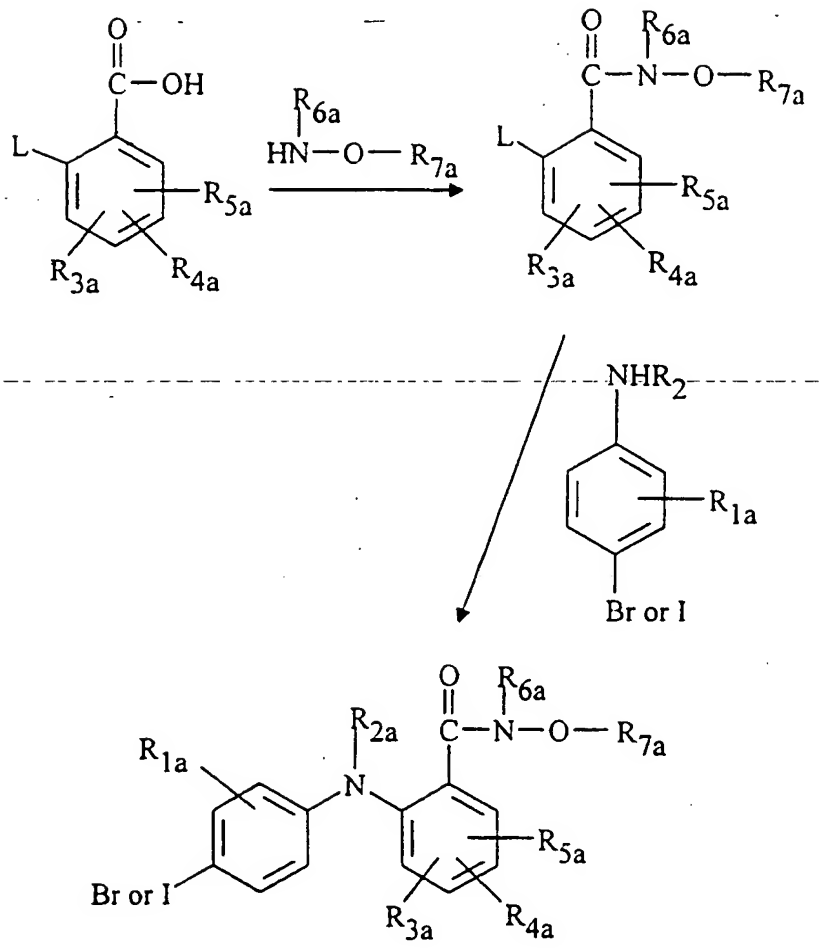
The reaction of aniline and the benzoic acid derivative generally is accomplished by mixing the benzoic acid with an equimolar quantity or excess of the aniline in an unreactive organic solvent such as tetrahydrofuran, or toluene, in the presence of a base such as lithium diisopropylamide, n-butyl lithium, sodium

hydride, and sodium amide. The reaction generally is carried out at a temperature of about -78°C to about 25°C, and normally is complete within about 2 hours to about 4 days. The product can be isolated by removing the solvent, for example by evaporation under reduced pressure, and further purified, if desired, by standard methods such as chromatography, crystallization, or distillation.

The phenylamino benzoic acid next is reacted with a hydroxylamine derivative $HNR_{6a}OR_{7a}$ in the presence of a peptide coupling reagent. Hydroxylamine derivatives that can be employed include methoxylamine, N-ethyl-isopropoxy amine, and tetrahydro-oxazine. Typical coupling reagents include 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), 1,3-dicyclohexylcarbodiimide (DCC), bromo-tris(pyrrolidino)-phosphonium hexafluorophosphate (PyBrOP) and (benzotriazolyloxy)tripyrrolidino phosphonium hexafluorophosphate (PyBOP). The phenylamino benzoic acid and hydroxylamino derivative normally are mixed in approximately equimolar quantities in an unreactive organic solvent such as dichloromethane, tetrahydrofuran, chloroform, or xylene, and an equimolar quantity of the coupling reagent is added. A base such as triethylamine or diisopropylethylamine can be added to act as an acid scavenger if desired. The coupling reaction generally is complete after about 10 minutes to 2 hours, and the product is readily isolated by removing the reaction solvent, for instance by evaporation under reduced pressure, and purifying the product by standard methods such as chromatography or crystallizations from solvents such as acetone, diethyl ether, or ethanol.

An alternative method for making the invention compounds involves first converting a benzoic acid to a hydroxamic acid derivative, and then reacting the hydroxamic acid derivative with an aniline. This synthetic sequence is depicted in Scheme 2.

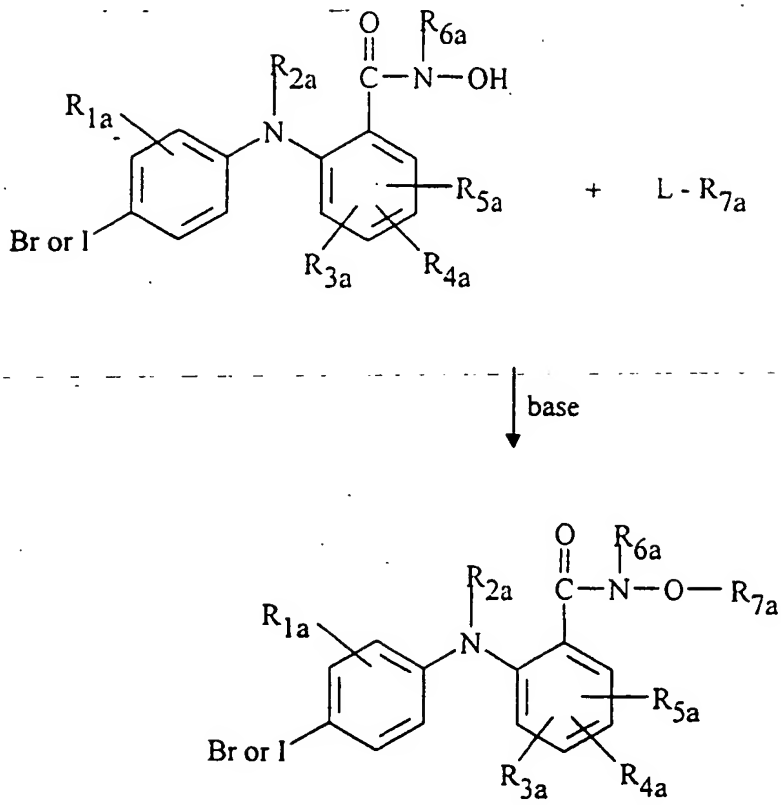
Scheme 2



where L is a leaving group. The general reaction conditions for both of the steps in Scheme 2 are the same as those described above for Scheme 1a.

Yet another method for making invention compounds comprises reacting a phenylamino benzhydroxamic acid with an ester forming group as depicted in Scheme 3.

Scheme 3



where L is a leaving group such as halo, and a base is triethylamine or diisopropylamine.

The synthesis of invention compounds of Formula II is further illustrated by the following detailed examples.

EXAMPLE 1a

4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

(a) Preparation of 4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

To a stirred solution containing 3.16 g (0.0133 mol) of 2-amino-5-iodotoluene in 5 mL of tetrahydrofuran at -78°C was added 10 mL (0.020 mol) of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for 15 minutes, after which time a solution of 1.00 g (0.00632 mol) of 2,4-difluorobenzoic acid in 10 mL of tetrahydrofuran was added. The reaction temperature was allowed to increase slowly to room temperature, at which

temperature the mixture was stirred for 2 days. The reaction mixture was concentrated by evaporation of the solvent under reduced pressure. Aqueous HCl (10%) was added to the concentrate, and the solution was extracted with dichloromethane. The organic phase was dried ($MgSO_4$) and then concentrated over a steambath to low volume (10 mL) and cooled to room temperature. The off-white fibers which formed were collected by vacuum filtration, rinsed with hexane, and dried in a vacuum-oven (76°C; ca. 10 mm of Hg) to afford 1.10 g (47%) of the desired material; mp 224-229.5°C;

^{1}H NMR (400 MHz, DMSO): δ 9.72 (s, 1H), 7.97 (dd, 1H, J=7.0, 8.7 Hz), 7.70 (d, 1H, J=1.5 Hz), 7.57 (dd, 1H, J=8.4, 1.9 Hz), 7.17 (d, 1H, J=8.2 Hz), 6.61-6.53 (m, 2H), 2.18 (s, 3H);

^{13}C NMR (100 MHz, DMSO): δ 169.87, 166.36 (d, J_{C-F}=249.4 Hz), 150.11 (d, J_{C-F}=11.4 Hz), 139.83, 138.49, 136.07, 135.26 (d, J_{C-F}=11.5 Hz), 135.07, 125.60, 109.32, 104.98 (d, J_{C-F}=21.1 Hz), 99.54 (d, J_{C-F}=26.0 Hz), 89.43, 17.52;

^{19}F NMR (376 MHz, DMSO): δ -104.00 to -104.07 (m);

IR (KBr) 1670 (C=O stretch)cm^{-1};

MS (CI) M+1 = 372.

Analysis calculated for $C_{14}H_{11}FINO_2$:

C, 45.31; H, 2.99; N, 3.77.

Found: C, 45.21; H, 2.77; N, 3.64.

(b) Preparation of 4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a stirred solution of 4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (0.6495 g, 0.001750 mol), O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (0.2590 g, 0.002211 mol), and diisopropylethylamine (0.40 mL, 0.0023 mol) in 31 mL of an equivolume tetrahydrofuran-dichloromethane solution was added 1.18 g (0.00227 mol) of solid PyBOP ([benzotriazolyloxy]tripyrrolidino phosphonium hexafluorophosphate, Advanced ChemTech) directly. The reaction mixture was stirred for 30 minutes after which time it was concentrated in vacuo.

The brown oil was treated with 10% aqueous hydrochloric acid. The suspension was extracted with ether. The organic extraction was washed with 10% sodium hydroxide followed by another 10% hydrochloric acid wash, was dried ($MgSO_4$) and concentrated in vacuo to afford 1.0 g of a light-brown foam. This intermediate was dissolved in 25 mL of ethanolic hydrogen chloride, and the solution was allowed to stand at room temperature for 15 minutes. The reaction mixture was concentrated in vacuo to a brown oil that was purified by flash silica chromatography. Elution with dichloromethane→dichloromethane-methanol (166:1) afforded 0.2284 g of a light-brown viscous oil. Scratching with pentane-hexanes and drying under high vacuum afforded 0.1541 g (23%) of an off-white foam; mp 61-75°C;

^{1}H NMR (400 MHz, DMSO): δ 11.34 (s, 1H), 9.68 (s, 1H), 9.18 (s, 1H), 7.65 (d, 1H, J=1.5 Hz), 7.58 (dd, 1H, J=8.7, 6.8 Hz), 7.52 (dd, 1H, J=8.4, 1.9 Hz), 7.15 (d, 1H, J=8.4 Hz), 6.74 (dd, 1H, J=11.8, 2.4 Hz), 6.62 (ddd, 1H, J=8.4, 8.4, 2.7 Hz), 2.18 (s, 3H);

^{13}C NMR (100 MHz, DMSO): δ 165.91, 164.36 (d, J_{C-F}=247.1 Hz), 146.78, 139.18, 138.77, 135.43, 132.64, 130.60 (d, J_{C-F}=11.5 Hz), 122.23, 112.52, 104.72 (d, J=22.1 Hz), 100.45 (d, J_{C-F}=25.2 Hz), 86.77, 17.03;

^{19}F NMR (376 MHz, DMSO): δ -107.20 to -107.27 (m);

IR (KBr) 3307 (broad, O-H stretch), 1636 (C=O stretch) cm^{-1};

MS (CI) M+1 = 387.

Analysis calculated for $C_{14}H_{12}FIN_2O_2$:

C, 43.54; H, 3.13; N, 7.25.

Found: C, 43.62; H, 3.24; N, 6.98.

EXAMPLE 2a

5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

(a) Preparation of 5-Bromo-2,3,4-trifluorobenzoic acid

To a stirred solution comprised of 1-bromo-2,3,4-trifluorobenzene (Aldrich, 99%; 5.30 g, 0.0249 mol) in 95 mL of anhydrous tetrahydrofuran cooled

to -78°C was slowly added 12.5 mL of 2.0 M lithium diisopropylamide in heptane/tetrahydrofuran/ethylbenzene solution (Aldrich). The mixture was stirred for 1 hour and transferred by canula into 700 mL of a stirred saturated ethereal carbon dioxide solution cooled to -78°C. The cold bath was removed, and the reaction mixture was stirred for 18 hours at ambient temperature. Dilute (10%) aqueous hydrochloric acid (ca. 500 mL) was poured into the reaction mixture, and the mixture was subsequently concentrated on a rotary evaporator to a crude solid. The solid product was partitioned between diethyl ether (150 mL) and aq. HCl (330 mL, pH 0). The aqueous phase was extracted with a second portion (100 mL) of diethyl ether, and the combined ethereal extracts were washed with 5% aqueous sodium hydroxide (200 mL) and water (100 mL, pH 12). These combined alkaline aqueous extractions were acidified to pH 0 with concentrated aqueous hydrochloric acid. The resulting suspension was extracted with ether (2 × 200 mL). The combined organic extracts were dried ($MgSO_4$), concentrated in vacuo, and subjected to high vacuum until constant mass was achieved to afford 5.60 g (88% yield) of an off-white powder; mp 139-142.5°C;

^1H NMR (400 MHz, DMSO): δ 13.97 (broad s, 1H, 8.00-7.96 (m, 1H);

^{13}C NMR (100 MHz, DMSO): δ 162.96, 129.34, 118.47, 104.54 (d, J_{C-F}=22.9 Hz);

^{19}F NMR (376 MHz, DMSO): δ -120.20 to -120.31 (m), -131.75 to -131.86 (m), -154.95 to -155.07 (m);

IR (KBr) 1696 (C=O stretch)cm^{-1};

MS (CI) M+1 = 255.

Analysis calculated for $C_{74}H_{21}BrF_3O_2$:

C, 32.97; H, 0.79; N, 0.00; Br, 31.34; F, 22.35.

Found: C, 33.18; H, 0.64; N, 0.01; Br, 30.14; F, 22.75.

(b) Preparation of 5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid

To a stirred solution comprised of 1.88 g (0.00791 mol) of 2-amino-5-iodotoluene in 10 mL of tetrahydrofuran at -78°C was added 6 mL (0.012 mol) of a 2.0 M lithium diisopropylamide in tetrahydrofuran/heptane/ethylbenzene (Aldrich) solution. The resulting green suspension was stirred vigorously for 10 minutes, after which time a solution of 1.00 g (0.00392 mol) of 5-bromo-2,3,4-trifluorobenzoic acid in 15 mL of tetrahydrofuran was added. The cold bath was subsequently removed, and the reaction mixture stirred for 18 hours. The mixture was concentrated, and the concentrate was treated with 100 mL of dilute (10%) aqueous hydrochloric acid. The resulting suspension was extracted with ether (2 × 150 mL), and the combined organic extractions were dried ($MgSO_4$) and concentrated in vacuo to give an orange solid. The solid was triturated with boiling dichloromethane, cooled to ambient temperature, and collected by filtration. The solid was rinsed with dichloromethane, and dried in the vacuum-oven (80°C) to afford 1.39 g (76%) of a yellow-green powder; mp 259.5-262°C;

^1H NMR (400 MHz, DMSO): δ 9.03 (s, 1H), 7.99 (dd, 1H, J=7.5, 1.9 Hz), 7.57 (dd, 1H, J=1.5 Hz), 7.42 (dd, 1H, J=8.4, 1.9 Hz), 6.70 (dd, 1H, J=8.4, 6.0 Hz), 2.24 (s, 3H);

^{19}F NMR (376 MHz, DMSO): δ -123.40 to -123.47 (m); -139.00 to -139.14 (m);

IR (KBr) 1667 (C=O stretch)cm^{-1};

MS (CI) M+1 = 469.

Analysis calculated for $C_{14}H_9BrF_2INO_2$:

C, 35.93; H, 1.94; N, 2.99; Br, 17.07; F, 8.12; I, 27.11.

Found: C, 36.15; H, 1.91; N, 2.70; Br, 16.40; F, 8.46; I, 26.05.

(c) Preparation of 5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide

To a stirred solution comprised of 5-bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid (0.51 g, 0.0011 mol), O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (0.15 g, 0.0013 mol), and diisopropylethylamine (0.25 mL, 0.0014 mol) in 20 mL of an equivolume tetrahydrofuran-

dichloromethane solution was added 0.6794 g (0.001306 mol) of solid PyBOP (Advanced ChemTech) directly. The reaction mixture was stirred at 24°C for 10 minutes, and then was concentrated to dryness in vacuo. The concentrate was suspended in 100 mL of 10% aqueous hydrochloric acid. The suspension was extracted with 125 mL of diethyl ether. The ether layer was separated, washed with 75 mL of 10% aqueous sodium hydroxide, and then with 100 mL of dilute acid. The ether solution was dried ($MgSO_4$) and concentrated in vacuo to afford 0.62 g (100%) of an off-white foam. The foam was dissolved in ca. 15 mL of methanolic hydrogen chloride. After 5 minutes, the solution was concentrated in vacuo to an oil, and the oil was purified by flash silica chromatography. Elution with dichloromethane→dichloromethane-methanol (99:1) afforded 0.2233 g (42%) of a yellow powder. The powder was dissolved in diethyl ether and washed with dilute hydrochloric acid. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to afford 0.200 g of a foam. This product was triturated with pentane to afford 0.1525 g of a powder that was repurified by flash silica chromatography. Elution with dichloromethane afforded 0.0783 g (15%) of an analytically pure title compound, mp 80-90°C;

^1H NMR (400 MHz, DMSO): δ 11.53 (s, 1H), 9.38 (s, 1H), 8.82 (s, 1H), 7.70 (dd, 1H, J=7.0, 1.9 Hz), 7.53 (s, 1H), 7.37 (dd, 1H, J=8.4, 1.9 Hz), 6.55 (dd, 1H, J=8.2, 6.5 Hz), 2.22 (s, 3H);

^{19}F NMR (376 MHz, DMSO): δ -126.24 to -126.29 (m), -137.71 to -137.77 (m);

IR (KBr) 3346 (broad, O-H stretch), 1651 (C=O stretch)cm^{-1};

MS (CI) M+1 = 484.

Analysis calculated for $C_{14}H_{10}BrF_2IN_2O_2$:

C, 34.81; H, 2.09; N, 5.80.

Found: C, 34.53; H, 1.73; N, 5.52,

Examples 3 to 12 in the table below were prepared by the general procedure of Examples 1a and 2a.

EXAMPLES 13a-77a

Examples 13 to 77 were prepared utilizing combinatorial synthetic methodology by reacting appropriately substituted phenylamino benzoic acids

(e.g., as shown in Scheme 1) and hydroxylamines (e.g., HN-O-R_{7a}). A general method is given below:

To a 0.8-mL autosampler vial in a metal block was added 40 µL of a 0.5 M solution of the acid in DMF and 40 µL of the hydroxylamine (2 M solution in Hunig's base and 1 M in amine in DMF). A 0.5 M solution of PyBrop was freshly prepared, and 50 µL were added to the autosampler vial. The reaction was allowed to stand for 24 hours.

The reaction mixture was transferred to a 2-dram vial and diluted with 2 mL of ethyl acetate. The organic layer was washed with 3 mL of distilled water and the water layer washed again with 2 mL of ethyl acetate. The combined organic layers were allowed to evaporate to dryness in an open fume hood.

The residue was taken up in 2 mL of 50% acetonitrile in water and injected on a semi-prep reversed phase column (10 mm × 25 cm, 5 µM spherical silica, pore Size 115 A derivatized with C-18, the sample was eluted at 4.7 mL/min with a linear ramp to 100% acetonitrile over 8.5 minutes. Elution with 100% acetonitrile continued for 8 minutes.) Fractions were collected by monitoring at 214 nM. The desired fractions were evaporated using a Zymark Turbovap. The product was dissolved in chloroform and transferred to a preweighed vial, evaporated, and weighed again to determine the yield. The structure was confirmed by mass spectroscopy.

EXAMPLES 3a-77a

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
3a	2-(4-bromo-2-methyl-phenylamino)-4-fluoro-N-hydroxy-benzamide	56-75 dec	523
4a	5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide	65 dec	
5a	5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide	62-67	
6a	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(terahydropyran-2-yloxy)benzamide	105-108	
7a	5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxybenzamide	64-68	
8a	4-Fluoro-N-hydroxy-2-(4-fluoro-2-methyl-phenylamino)-benzamide	119-135	
9a	4-Fluoro-N-hydroxy-2-(2-methyl phenylamino)-benzamide	101-103	
10a	4-Fluoro-2-(4-fluor-2-methyl-phenylamino)-N-(terahydropyran-2-yloxy)benzamide	142-146	
11a	4-Fluoro-N-hydroxy-2-(4-cluoro-2-methyl-phenylamino)-benzamide	133.5-135	

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
12a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide	107-109.5	
13a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide		399
14a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide		417
15a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-methoxy-benzamide		369
16a	2-(4-Bromo-2-methyl-phenylamino)-N-ethoxy-3,4-difluoro-benzamide		342* (M-EtO)
17a	5-Bromo-N-ethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		509
18a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		445
19a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-isopropoxy-benzamide		397
20a	4-Fluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		465

Example No.	Compound	Melting Point (°C)	MS (M-H$^+$)
21a	3,4-Difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		483
22a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(furan-3-ylmethoxy)-benzamide		435
23a	5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide		561
24a	5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		536
25a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide		423
26a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide		441
27a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1-methyl-prop-2-ynyloxy)-benzamide		455
28a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(1-methyl-prop-2-ynyloxy)-benzamide		407
29a	N-(But-3-ynyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		455

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
30a	2-(4-Bromo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-3,4-difluoro-benzamide		407
31a	5-Bromo-N-(but-3-ynyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		533
32a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenyl-prop-2-ynyloxy)-benzamide		517
33a	3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-phenyl-prop-2-ynyloxy)-benzamide		469
34a	3,4-Difluoro-N-[3-(3-fluoro-phenyl)-prop-2-ynyloxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide		535
35a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-[3-(3-fluoro-phenyl)-prop-2-ynyloxy]-benzamide		487
36a	3,4-Difluoro-N-[3-(2-fluoro-phenyl)-prop-2-ynyloxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide		535
37a	5-Bromo-3,4-difluoro-N-[3-(2-fluoro-phenyl)-prop-2-ynyloxy]-2-(4-iodo-2-methyl-phenylamino)-benzamide		613

Example No.	Compound	Melting Point (°C)	MS (M-H$^+$)
38a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenyl-pent-2-en-4-ynyloxy)-benzamide		557* *(M+H)
39a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-methyl-5-phenyl-pent-2-en-4-ynyloxy)-benzamide		510
40a	N-Ethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		431
41a	2-(4-Bromo-2-methyl-phenylamino)-N-ethoxy-3,4-difluoro-benzamide		383
42a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propoxy-benzamide		427
43a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-propoxy-benzamide		445
44a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-propoxy-benzamide		397
45a	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-propoxy-benzamide		523
46a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		427

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
47a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		445
48a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-isopropoxy-benzamide		397
49a	5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-isopropoxy-benzamide		523
50a	N-Cyclobutyloxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457
51a	2-(4-Bromo-2-methyl-phenylamino)-N-cyclobutyloxy-3,4-difluoro-benzamide		409
52a	N-Cyclopentyloxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		453
53a	N-Cyclopentyloxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		471
54a	2-(4-Bromo-2-methyl-phenylamino)-N-cyclopentyloxy-3,4-difluoro-benzamide		423
55a	N-Cyclopropylmethoxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		439
56a	N-Cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457

Example No.	Compound	Melting Point (°C)	MS (M-H$^+$)
57a	2-(4-Bromo-2-methyl-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide		409
58a	5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)		435
59a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxy-ethoxy)-benzamide		505
60a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxy-ethoxy)-benzamide		523
61a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-phenoxy-ethoxy)-benzamide		475
62a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiophen-2-ylmethoxy)-benzamide		481
63a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiophen-2-ylmethoxy)-benzamide		499
64a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(thiophen-2-ylmethoxy)-benzamide		451
65a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-allyloxy)-benzamide		439

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
66a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-allyloxy)-benzamide		457
67a	2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-methyl-allyloxy)-benzamide		410
68a	N-(But-2-enyloxy)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		439
69a	N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457
70a	2-(4-Bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-3,4-difluoro-benzamide		410
71a	3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide		441
72a	N-(But-3-ynyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		455
73a	2-(4-Bromo-2-methyl-phenylamino)-N-(4,4-dimethyl-pent-2-ynyloxy)-3,4-difluoro-benzamide		449
74a	N-(But-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		457

Example No.	Compound	Melting Point (°C)	MS ($M-H^+$)
75a	2-(4-Bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-3,4-difluoro-benzamide		410
76a	N-(3-tert.-butyl-propyn-2-yl)oxy-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide		479
77a	4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide		577* *Cl

Enzyme Assays

Cascade assay for inhibitors of the MAP kinase pathway

Incorporation of ^{32}P into myelin basic protein (MBP) was assayed in the presence of a glutathione S-transferase fusion protein containing p44MAP kinase (GST-MAPK) and a glutathione S-transferase fusion protein containing p45MEK (GST-MEK). The assay solution contained 20 mM HEPES, pH 7.4, 10 mM $MgCl_2$, 1 mM $MnCl_2$, 1 mM EGTA, 50 µM [γ-^{32}P]ATP, 10 µg GST-MEK, 0.5 µg GST-MAPK and 40 µg MBP in a final volume of 100 µL. Reactions were stopped after 20 minutes by addition of trichloroacetic acid and filtered through a GF/C filter mat. ^{32}P retained on the filter mat was determined using a 1205 Betaplate. Compounds were assessed at 10 µM for ability to inhibit incorporation of ^{32}P.

To ascertain whether compounds were inhibiting GST-MEK or GST MAPK, two additional protocols were employed. In the first protocol, compounds were added to tubes containing GST-MEK, followed by addition of GST-MAPK, MBP and [γ-^{32}P]ATP. In the second protocol, compounds were added to tubes containing both GST-MEK and GST-MAPK, followed by MBP and [γ-^{32}P]ATP.

Compounds that showed activity in both protocols were scored as MAPK inhibitors, while compounds showing activity in only the first protocol were scored as MEK inhibitors.

In vitro MAP kinase assay

Inhibitory activity was also confirmed in direct assays. For MAP kinase, 1 µg GST-MAPK was incubated with 40 µg MBP for 15 minutes at 30°C in a final volume of 50 µL containing 50 mM Tris (pH 7.5), 10 µM $MgCl_2$, 2 µM EGTA, and 10 µM [γ-^{32}P]ATP. The reaction was stopped by addition of Laemmli SDS sample buffer and phosphorylated MBP resolved by electrophoresis on a 10% polyacrylamide gel. Radioactivity incorporated into MBP was determined by autoradiography, and subsequently by excision of the bands followed by scintillation counting.

In vitro MEK assay

For evaluation of direct MEK activity, 10 µg GST-MEK_1 was incubated with 5 µg of a glutathione S-transferase fusion protein containing p44MAP kinase with a lysine to alanine mutation at position 71 (GST-MAPK-KA). This mutation eliminates kinase activity of MAPK, so only kinase activity attributed to the added MEK remains. Incubations were 15 minutes at 30°C in a final volume of 50 µL containing 50 mM Tris (pH 7.5), 10 µM $MgCl_2$, 2 µM EGTA, and 10 µM [γ-^{32}P]ATP. The reaction was stopped by addition of Laemmli SDS sample buffer and phosphorylated GST-MAPK-KA was resolved by electrophoresis on a 10% polyacrylamide gel. Radioactivity incorporated into GST-MAPK-KA was determined by autoradiography, and subsequently by excision of the bands followed by scintillation counting. Additionally, an artificially activated MEK was utilized that contained serine to glutamate mutations at positions 218 and 222 (GST-MEK-2E). When these sites are phosphorylated, MEK activity is increased. Phosphorylation of these sites can be mimicked by mutation of the serine residues to glutamate. For this assay, 5 µg GST-MEK-2E was incubated

with 5 µg GST-MAPK-KA for 15 minutes at 30°C in the same reaction buffer as described above. Reactions were terminated and analyzed as above.

Whole cell MAP kinase assay

To determine if compounds were able to block activation of MAP kinase in whole cells, the following protocol was used: Cells were plated in multi-well plates and grown to confluence. Cells were then serum-deprived overnight. Cells were exposed to the desired concentrations of compound or vehicle (DMSO) for 30 minutes, followed by addition of a growth factor, for example, PDGF (100 ng/mL). After a 5-minute treatment with the growth factor, cells were washed with PBS, then lysed in a buffer consisting of 70 mM NaCl, 10 mM HEPES (pH 7.4), 50 mM glycerol phosphate, and 1% Triton X-100. Lysates were clarified by centrifugation at 13,000 × g for 10 minutes. Five micrograms of the resulting supernatants were incubated with 10 µg microtubule associated protein-2 (Map2) for 15 minutes at 30°C in a final volume of 25 µL containing 50 mM Tris (pH 7.4), 10 mM $MgCl_2$, 2 mM EGTA and 30 µM [γ-^{32}P]ATP. Reactions were terminated by addition of Laemmli sample buffer. Phosphorylated Map2 was resolved on 7.5% acrylamide gels and incorporated radioactivity determined by autoradiography and subsequent excision of the bands followed by scintillation counting.

Immunoprecipitation and antiphosphotyrosine immunoblots

To determine the state of tyrosine phosphorylation of cellular MAP kinase, cells were lysed, endogenous MAP kinase was immunoprecipitated with a specific antibody, and the resulting immunoprecipitate analyzed for the presence of phosphotyrosine as follows: confluent cells were serum-deprived overnight and treated with compounds and growth factors as described above. Cells were then scraped and pelleted at 13,000 × g for 2 minutes. The resulting cell pellet was resuspended and dissolved in 100 µL of 1% SDS containing 1 mM $NaVO_4$. Following alternate boiling and vortexing to denature cellular protein, 900 µL RIPA buffer (50 mM Tris (pH 7.4), 150 mM NaCl, 1% Triton X-100, 0.1%

deoxycholate, and 10 mM EDTA) was added. To this mixture was added 60 µL agarose beads coupled with rabbit immunoglobulin G and 60 µL Pansorbin cells in order to clear the lysate of nonspecific binding proteins. This mixture was incubated at 4°C for 15 minutes then centrifuged at 13,000 × g for 10 minutes. The resulting supernatant was transferred to fresh tubes and incubated with 10 µL of a polyclonal antisera raised against a fragment of MAP kinase for a minimum of 1 hour at 4°C. Seventy microliters of a slurry of agarose beads coupled with protein G and protein A was added and the incubation continued for an additional 30 minutes at 4°C. The beads were pelleted by centrifugation at 13,000 × g for 5 minutes and washed three times with 1 mL RIPA buffer. Laemmli sample buffer was added to the final bead pellet. This mixture was boiled for 5 minutes then resolved on a 10% acrylamide gel. Proteins on the gel were transferred to a nitrocellulose membrane and nonspecific binding sites on the membrane blocked by incubation with 1% ovalbumin and 1% bovine serum albumin in TBST (150 mM NaCl, 10 mM Tris (pH 7.4), and 0.05% Tween 20). The membrane was then incubated with a commercially available antibody directed against phosphotyrosine. Antibody bound on the membrane was detected by incubation with ^{125}I-protein A, followed by autoradiography.

Cell Growth Assays

^{3}H-Thymidine incorporation

Cells were plated in multi-well plates and grown to near confluence. The media was then removed and replaced with growth media containing 1% bovine serum albumin. After 24-hour serum starvation, compounds and specific growth factors were added and incubations continued for an additional 24 hours. During the final 2 hours, ^{3}H-thymidine was added to the medium. To terminate the incubations, the medium was removed and cell layers washed twice with ice-cold phosphate-buffered saline. After the final wash, ice-cold 5% trichloroacetic acid was added and the cells incubated for 15 minutes at room temperature. The trichloroacetic acid solution was then removed and the cell layer washed three

times with distilled water. After the final wash, the cell layer was solubilized by addition of 2% sodium dodecylsulfate. Radioactivity in this solution was determined by scintillation counting.

In 3T3-L1 adipocyte cells, in which the inhibition blocks MAPK activation by insulin with an IC_{50} of 3 μM, the compound had no effect on the insulin stimulated uptake of radiolabeled 2-deoxyglucose, or on the insulin-stimulated synthesis of either lipid or glycogen at 10 μM concentration. This demonstrates that the inhibitor shows selectivity between the mitogenic and metabolic effects of insulin, and demonstrates that the inhibitor will show less toxicity than an inhibitor which does not show this surprising selectivity.

Monolayer growth

Cells were plated into multi-well plates at 10 to 20,000 cells/mL. Forty-eight hours after seeding, compounds were added to the cell growth medium and incubation was continued for 2 additional days. Cells were then removed from the wells by incubation with trypsin and enumerated with a Coulter counter.

Growth in soft-agar

Cells were seeded into 35-mm dishes at 5 to 10,000 cells/dish using growth medium containing 0.3% agar. After chilling to solidify the agar, cells were transferred to a 37°C incubator. After 7 to 10 days growth, visible colonies were manually enumerated with the aid of a dissecting microscope.

Order of addition experiments established that the invention compounds are inhibiting MEK and not MAP kinase. Experiments looking at the phosphorylation of a kinase defective mutant of MAP kinase as substrate (so that there can be no autophosphorylation of the MAP kinase to complicate interpretation) confirms that the inhibitor inhibits MEK with an IC_{50} essentially identical to that produced in the cascade assay.

Kinetic analysis demonstrates that the invention compounds are not competitive with ATP. Thus, they do not bind at the ATP binding site of the enzyme, which is probably the explanation as to why these compounds do not

show the nonspecific kinase inhibitory activity typical of most kinase inhibitors, which do bind at the ATP binding site and which are ATP competitive.

The in vitro and in vivo biological activity of several representative compounds of Formula I and II in the foregoing assays is presented in Tables 1 and 2.

TABLE 1

Compound of	In Vitro		In Vivo	
Example No.	% Inhibition	IC_{50} μM	% Inhibition	IC_{50} μM
4		0.005		1
3		0.0111		10
2		0.014		3
1		0.019		
32		0.028		
53		0.047		0.54
33		0.052		
5		0.066		
6		0.071		
7		0.072		
8		0.086		
9		0.097		
34		0.098		
10		0.101		
55		0.114		
35		0.121		
11		0.128		
36		0.129		
12		0.135		
54		0.158		
13		0.178		

TABLE 1

Compound of	In Vitro		In Vivo	
Example No.	% Inhibition	IC_{50} μM	% Inhibition	IC_{50} μM
14		0.179		
15		0.194		
31		0.226		
37		0.237		
92		0.253		
184		0.278		
16		0.323		
96		0.374		
57		0.399		
38		0.412		
49		0.418		3
17		0.434		
18		0.446		
91		0.449		
39		0.497		
93		0.521		
19		0.524	50% at 30 μM	
186		0.555		
20		0.557		
187		0.561		
21		0.569		
90		0.604		
89		0.614		
40		0.651	30% at 30 μM	
188		0.771		
189		0.859		
41		0.872		
51		0.887		

TABLE 1

Compound of	In Vitro		In Vivo	
Example No.	% Inhibition	IC_{50} µM	% Inhibition	IC_{50} µM
42		0.920		
190		0.921		
43		>1.000		
95		1.001		
208		1.215		
191		1.355		
209		1.372		
44		1.481		
22		1.581	30% at 30 µM	
23		1.588		
45		1.755		
192		1.797		
46		1.814		
47		1.911		
24		1.944		
48		1.945		
100		1.994		
91		2.071		
27		2.269		
52		2.346		
25		2.363		
26		2.609	50% at 30 µM	
193		2.902		
28		3.670		
194		4.952		
29		5.331		
195		12.831		
30		105		10

TABLE 2

Compound of Example No.	In vitro IC_{50} (μM)	In vivo IC_{50} (μM)
1a	0.007	0.05
2a	0.003	0.03
3a	0.072	3
4a	0.023	1
5a	0.566	~30
6a	0.345	~30
7a	0.221	<30
8a	7.13	3
9a	0.409	1
11a	0.334	0.5
12a	0.826	
13a	0.243	
14a	0.061	>2
17a	0.014	
20a	0.042	0.17
21a	0.014	
22a	0.137	
23a	0.016	
24a	0.021	0.12
25a	0.102	
27a	0.026	
28a	0.728	
29a	0.076	0.73
30a	0.971	
31a	0.045	
32a	0.017	
33a	0.374	
34a	0.113	1.5
36a	0.056	0.07

TABLE 2

Compound of Example No.	In vitro IC_{50} (μM)	In vivo IC_{50} (μM)
40a	0.028	0.125
41a	0.236	
42a	0.087	
43a	0.040	0.100
44a	0.475	
45a	0.126	
47a	0.087	0.13
49a	0.085	
50a	0.043	0.22
53a	0.140	
55a	0.047	
56a	0.014	
57a	0.181	
58a	0.018	0.014
59a	0.259	
62a	0.086	
63a	0.019	
64a	0.279	
65a	0.057	
66a	0.016	0.13
68a	0.119	
69a	0.016	
70a	0.224	
71a	0.015	0.39
74a	0.035	
77a	0.28	

CLAIMS

What is claimed is:

1. A method of treating or preventing septic shock, the method comprising administering to a patient having septic shock or at risk of having septic shock a therapeutically acceptable amount of a compound that is a MEK inhibitor.

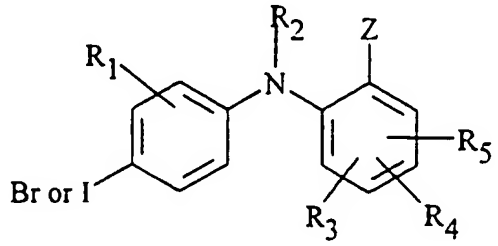
2. The method of Claim 1 wherein the compound is 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran.

3. The method of Claim 1 wherein the patient has septic shock.

4. The method of Claim 1 wherein the patient is at risk of having septic shock.

5. A method of treating or preventing septic shock, the method comprising administering to a patient having septic shock or at risk of having septic shock a therapeutically acceptable amount of 2-(2-amino-3-methoxyphenyl)-4-oxo-4H-[1]benzopyran.

6. The method of Claim 1 wherein the MEK inhibitor is a compound of Formula I



I

wherein:

R_1 is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN;

R_2 is hydrogen;

R_3, R_4, and R_5 independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, or -(O or NH)$_m$-$(CH_2)_n$-R_9, where R_9 is hydrogen, hydroxy, COOH, or $NR_{10}R_{11}$;

n is 0-4;

m is 0 or 1;

R_{10} and R_{11} independently are hydrogen or C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N-C_1-C_8 alkyl;

Z is $COOR_7$, tetrazolyl, $CONR_6R_7$, $CONHNR_{10}R_{11}$, or CH_2OR_7;

R_6 and R_7 independently are hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C(=O)-C_1-C_8 alkyl, aryl, heteroaryl, C_3-C_{10} cycloalkyl, or C_3-C_{10} (cycloalkyl optionally containing one, two, or three heteroatoms selected from O, S, NH, or N alkyl); or R_6 and R_7 together with the nitrogen to which they are attached complete a 3-10 member cyclic ring optionally containing 1, 2, or 3 additional heteroatoms selected from O, S, NH, or N alkyl;

and wherein any of the foregoing alkyl, alkenyl, and alkynyl groups can be unsubstituted or substituted by halo, hydroxy, alkoxy, amino, alkylamino, dialkylamino, cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy, and the pharmaceutically acceptable salts, esters, amides, or prodrugs thereof.

7. The method of Claim 6 wherein the MEK inhibitor is

[4-Chloro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine;

(4-iodo-2-methyl-phenyl)-[2-(1H-tetrazol-5-yl)-phenyl]amine;

[4-nitro-2-(1H-tetrazol-5-yl)-(4-iodo-2-methyl-phenyl)-amine;

4-Fluoro-2-(4-iodo-2-methylphenylamino)benzoic acid;

3,4,5-Trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

Sodium 5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoate;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-benzoic acid;

4-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-benzoic acid;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2,3,5-Trifluoro-4-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-phenylamino)-5-methoxy-benzoic acid;

5-Methyl-2-(4-iodo-2-methyl-phenylamino)-benzoic acid;

2-(4-Iodo-2-methyl-phenylamino)-4-nitro-benzoic acid;

2-(4-Bromo-2-methyl-phenylamino)-4-fluoro-benzoic acid;

2-(2-Bromo-4-iodo-phenylamino)-5-nitro-benzoic acid;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-benzoic acid;

5-Chloro-N-(2-hydroxyethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-benzamide;

N-Ethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1H-tetrazol-5-yl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-benzoylamino]-acetic acid;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-propyl-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N,N-Diethyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Butyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N,N-diethyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N,N-dimethyl-benzamide;

5-Bromo-3,4-difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

3,4-Difluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2,3-Dihydroxy-propyl)-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

3,4-Difluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

4-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3-dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

N-(3-Dimethylamino-propyl)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyl-4-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-hydroxy-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thiophen-2-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-N-(3-dimethylamino-propyl)-3,4-difluoro-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyridin-4-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyridin-4-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(3-hydroxy-propyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-thiophen-2-yl-ethyl)-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-pyridin-4-ylmethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-phenethyl-benzamide;

2-(4-Bromo-2-methyl-phenylamino)-3,4-difluoro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Chloro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Fluoro-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-pyridin-4-yl methyl-benzamide;

5-Bromo-N-{3-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Chloro-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

(3-Hydroxy-pyrrolidin-1-yl)-[2-(4-iodo-2-methyl-phenylamino)-5-nitro-phenyl];

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(2-diethylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-chloro-2-(4-iodo-2-methyl- phenylamino)- benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-bromo-2-(4-iodo-2-methyl- phenylamino)- benzamide;

N-{3-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-propyl}-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-pyridin-4-ylmethyl-benzamide;

5-Bromo-2-(4-iodo-2-ethyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-pyrrolidin-1-yl-ethyl)-benzamide;

5-Chloro-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-5-fluoro-2-(4-iodo-2-methyl- phenylamino)- benzamide;

5-Chloro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(3-diethylamino-2-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)- benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

N-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(4-iodo-2-methyl-phenylamino)-5-nitro- benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Chloro-N-(3-diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(2-piperidin-1-yl-ethyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-piperazin-1-yl-ethyl)-benzamide;

N-(2-Diethylamino-ethyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(3-dimethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(3-hydroxy-propyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Diethylamino-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(3-Diethylamino-propyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(3-piperidin-1-yl-propyl)-benzamide;

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-(3-hydroxy-pyrrolidin-1-yl)-;

5-Bromo-N-(2-diisopropylamino-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-morpholin-4-yl-ethyl)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-piperidin-1-yl-propyl)-benzamide;

[5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-[4-(2-hydroxy-ethyl)-piperazin-1-;

N-(3-Diethylamino-2-hydroxy-propyl)-5-fluoro-2-(4-iodo-2-methyl-phenylamino)- benzamide;

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-ethyl-phenylamino)-5-nitro-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-5-nitro-N-(4-sulfamoyl-benzyl)-benzamide;

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclopropyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Benzyloxy-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Cyclohexyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-5-nitro-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Cyclohexyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

5-Bromo-N-cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-benzyl)-benzamide;

N-Cyclohexyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Benzyloxy-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

2-(4-Iodo-2-methyl-phenylamino)-N-methyl-5-nitro-N-phenyl-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-(2-Hydroxy-ethyl)-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-chloro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-(2-Hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

5-Fluoro-N-(2-hydroxy-ethyl)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Cyclopropyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

N-Cyclopropyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

N-Allyl-5-fluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Benzyloxy-5-iodo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

N-Allyl-5-bromo-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-(4-sulfamoyl-benzyl)-benzamide;

5-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-methyl-N-phenyl-benzamide;

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-benzyl alcohol;

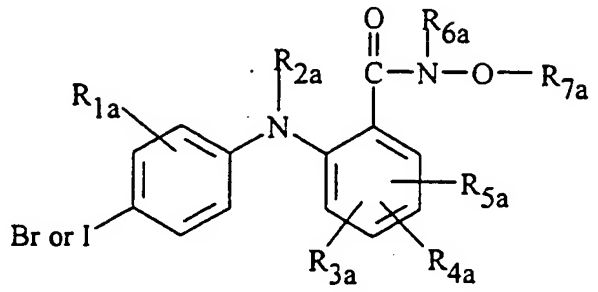
[5-Chloro-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol;

[2-(4-Iodo-2-methyl-phenylamino)-5-nitro-phenyl]-methanol;

[5-Bromo-2-(4-iodo-2-methyl-phenylamino)-phenyl]-methanol; or

N-Allyl-2-(4-iodo-2-methyl-phenylamino)-5-nitro-benzamide.

8. The method of Claim 1 wherein the MEK inhibitor is a compound of Formula II



II

wherein:

R_{1a} is hydrogen, hydroxy, C_1-C_8 alkyl, C_1-C_8 alkoxy, halo, trifluoromethyl, or CN;

R_{2a} is hydrogen;

R_{3a}, R_{4a}, and R_{5a} independently are hydrogen, hydroxy, halo, trifluoromethyl, C_1-C_8 alkyl, C_1-C_8 alkoxy, nitro, CN, or $(O \text{ or } NH)_m$-$(CH_2)_n$-R_{9a}, where R_{9a} is hydrogen, hydroxy, CO_2H or $NR_{10a}R_{11a}$.

n is 0-4;

m is 0 or 1;

R_{10a} and R_{11a} independently are hydrogen or C_1-C_8 alkyl, or taken together with the nitrogen to which they are attached can complete a 3- to 10-member cyclic ring optionally containing one, two, or three additional heteroatoms selected from O, S, NH, or N-C_1-C_8 alkyl;

R_{6a} is hydrogen, C_1-C_8 alkyl, C-C_1-C_8 alkyl, aryl, aralkyl, or C_3-C_{10} cycloalkyl;

R_{7a} is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_3-C_{10} (cycloalkyl or cycloalkyl optionally containing a heteroatom selected from O, S, or NR_{9a});

and wherein any of the foregoing alkyl, alkenyl, and alkynyl groups can be unsubstituted or substituted by cycloalkyl, aryl, aryloxy, heteroaryl, or heteroaryloxy; or R_{6a} and R_{7a} taken together with the N to which they are attached can complete a 5- to 10-membered cyclic ring, optionally containing one, two, or three additional heteroatoms selected from O, S, or $NR_{10a}R_{11a}$, and the pharmaceutically acceptable salts, esters, amides or prodrugs thereof.

9. The method of Claim 1 wherein the MEK inhibitor is

4-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(methoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-enyloxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-ethoxy-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(1-methylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-5-phenylpent-2-en-4-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(propoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclobutyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopentyloxy)-benzamide;

3,4-Difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide;

5-Bromo-3,4-difluoro-N-(furan-3-ylmethoxy)-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-(but-2-enyloxy)-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide

5-Bromo-N-butoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-but-2-enyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-methyl-pent-2-en-4-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-benzyl)-N-[5-(3-methoxy-phenyl)-3-methyl-pent-2-en-4-ynyloxy]-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-[3-(3-methoxy-phenyl)-prop-2-ynyloxy]-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(thiopen-2-ylmethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(pyridin-3-ylmethoxy)-benzamide;

5-Bromo-3-4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(3-(2-fluorophenyl)-prop-2-ynyloxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(cyclopropylmethoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide;

5-Bromo-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-N-but-3-ynyloxy)-benzamide;

5-Chloro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydro-pyran-2-yloxy)-benzamide;

5-Chloro-2-(4-iodo-2-methyl-phenylamino)-N-methoxy-benzamide;

4-Bromo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

4-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

5-Fluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Iodo-2-(4-iodo-2-methyl-phenylamino)-N-phenylmethoxy-benzamide;

5-Fluoro-2-(4-iodo-2-methyl-phenylamino)-N-(tetrahydropyran-2-yloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-phenylprop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-furylmethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-thienylmethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-3-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-methyl-prop-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(but-2-enyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(methoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(ethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclobutoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(isopropoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(2-phenoxyethoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopropyl-methoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(n-propoxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(1-methyl-prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(3-(3-fluorophenyl)-prop-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(4,4-dimethylpent-2-ynyloxy)-benzamide;

3,4-Difluoro-2-(4-bromo-2-methyl-phenylamino)-N-(cyclopentoxy)-benzamide;

3,4,5-Trifluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-3,4-difluoro-N-hydroxy-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

N-Hydroxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide;

3,4,5-Trifluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

5-Chloro-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Fluoro-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-hydroxy-4-methyl-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-3,4,5-trifluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-hydroxy-4-nitro-benzamide;

4-Fluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

3,4-Difluoro-2-(2-fluoro-4-iodo-phenylamino)-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-4-fluoro-N-hydroxy-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-3,4-difluoro-N-hydroxy-benzamide;

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(4-iodo-2-methyl-phenylamino)-benzamide;

5-Bromo-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-Cyclopropylmethoxy-2-(4-iodo-2-methyl-phenylamino)-4-nitro-benzamide;

N-Cyclopropylmethoxy-3,4,5-trifluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Chloro-N-cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

5-Bromo-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

N-Cyclopropylmethoxy-2-(2-fluoro-4-iodo-phenylamino)-4-nitro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

5-Chloro-2-(2-chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

5-Bromo-2-(2-bromo-4-iodo-phenylamino)-N-ethoxy-3,4-difluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-ethoxy-4-nitro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4,5-trifluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-5-chloro-N-cyclopropylmethoxy-3,4-difluoro-benzamide

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-nitro-benzamide;

N-Cyclopropylmethoxy-4-fluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

N-Cyclopropylmethoxy-3,4-difluoro-2-(2-fluoro-4-iodo-phenylamino)-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide;

2-(2-Chloro-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide;

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-4-fluoro-benzamide; or

2-(2-Bromo-4-iodo-phenylamino)-N-cyclopropylmethoxy-3,4-difluoro-benzamide.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 97/23389

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/195 A61K31/165 A61K31/135 A61K31/41 A61K31/495
A61K31/445 A61K31/40 A61K31/44 A61K31/535 A61K31/38
A61K31/34 A61K31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 97 22704 A (SIGNAL PHARM INC) 26 June 1997 see abstract see page 13, line 15 - line 18 see page 17, line 27 - line 31; claims 17,25 ---	1,3,4
P,X	J.T. VAN DER BRUGGEN ET AL.: "MODULATION OF ENDOTOXIN-INDUCED TUMOR NECROSIS FACTOR alpha RELEASE BY HUMAN MONOCYTES" EUROPEAN JOURNAL OF CLINICAL INVESTIGATION, vol. 27, no. S1, March 1997, page A19 XP002063632 see abstract --- -/--	1-5

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
28 April 1998	27.05.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoff, P

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INTERNATIONAL SEARCH REPORT

Inte: ›nal Application No
PCT/US 97/23389

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	T.D. GEPPERT ET AL.: "LIPOPOLYSACCHARIDE SIGNALS ACTIVATION OF TUMOR NECROSIS FACTOR BIOSNTHESIS THROUGH THE RAS/RAF-1/MEK/MAPK PATHWAY" MOLECULAR MEDICINE, vol. 1, no. 1, 1994, pages 93-103, XP002063633 see the whole document	1-5
Y	WO 96 22985 A (WARNER LAMBERT CO) 1 August 1996 cited in the application see the whole document	1-5
Y	D.T. DUDLEY ET AL.: "A SYNTHETIC INHIBITOR OF THE MITOGEN-ACTIVATED PROTEIN KINASE CASCADE" PROC. NATL. ACAD. SCI., vol. 92, no. 17, 1995, pages 7686-7689, XP002063634 see the whole document	1-5
A	WO 96 36642 A (DERIJARD BENOIT ;RAINGEAUD JOEL (FR); DAVIS ROGER J (US); GUPTA SH) 21 November 1996 see abstract see page 9, line 16 - line 30 see claims	1
A	H. BEKEMEIER ET AL.: "STRUCTURE-ACTIVITY RELATIONSHIP IN NONSTEROIDAL ANTIINFLAMMATORY AGENTS, INCLUDING QSAR IN FENAMATE DERIVATIVES" AGENTS ACTIONS SUPPL., 1982, pages 17-34, XP002063635 see compound 15, table 1, page 25	6,7
A	P. RAMANUJAM ET AL.: "ANTIFUNGAL ACTIVITY OF SOME N-SUBSTITUTED ANTHRANILIC ACID DERIVATIVES" PLANTA MEDICA, vol. 25, no. 1, 1974, pages 43-46, XP002063636 see the whole document, in particular compound 6, table I, page 44	6,7
A	N.H. BERNER ET AL.: "SUBSTITUTED N-PHENYLANTHRANILIC ACID HYDRAZIDES AS POTENTIAL ANTIMALARIAL AND ANTIMICROBIAL AGENTS" JOURNAL OF MEDICINAL CHEMISTRY, vol. 13, no. 3, 1970, pages 552-554, XP002063637 see the whole document	6,7

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
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C.(Continuation) D CUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 103, no. 11, 16 September 1985 Columbus, Ohio, US; abstract no. 87588, A.N. GAIDUKEVICH ET AL.: "SYNTHESIS AND BIOLOGICAL ACTIVITY OF N-PHENYLANTHRANILIC ACID" XP002063638 see abstract & KHIM.-FARM. ZH., vol. 19, no. 3, 1985, pages 165-168, ---	6,7
A	CHEMICAL ABSTRACTS, vol. 109, no. 17, 24 October 1988 Columbus, Ohio, US; abstract no. 149000, T.I. SHUL'GA ET AL.: "SYNTHESIS AND PHYSICOCHEMICAL AND BIOLOGICAL PROPERTIES OF DIPHENYLAMINE-2-CARBOXYLIC ACID DERIVATIVES" XP002063639 see abstract & FARM. ZH., vol. 1, 1988, pages 42-45, ---	6,7
A	CHEMICAL ABSTRACTS, vol. 77, no. 19, 6 November 1972 Columbus, Ohio, US; abstract no. 122522, I.S. SHUL'GA ET AL.: "SYNTHESIS OF 6-NITRODIPHENYLAMINE-2-CARBOXYLIC ACID DERIVATIVES THEIR PHYSICOCHEMICAL AND ANTIMICROBIAL PROPERTIES" XP002063640 see abstract & FARM. ZH., vol. 27, no. 3, 1972, pages 84-85, -----	6,7

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I. .ational application No.
PCT/US 97/23389

Box I Ob ervations where certain laims were found unsear hable (Continuation of item 1 f first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: -

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

In view of the large number of compounds which are theoretically contained within the definition "MEK inhibitor" of claim 1, the search had to be restricted on economic ground to the compounds mentioned in claims 2,5-9 (Article 6 PCT; Guidelines Part B, Chapt.II.7 last sentence and Chapt.III, 3.7).

Claims searched completely: 2,5-9

Claims searched incompletely: 1,3,4

Remark : Although claims 1-9
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Inte ohal Application No
PCT/US 97/23389

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9722704 A	26-06-97	AU 1436797 A	14-07-97
WO 9622985 A	01-08-96	US 5525625 A	11-06-96
		AU 4245696 A	14-08-96
		CA 2208075 A	01-08-96
		EP 0805807 A	12-11-97
WO 9636642 A	21-11-96	US 5736381 A	07-04-98
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